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THE CARDIORESPIRATORY AND BIOCHEMICAL EVENTS DURING RAPID ANOXIC DEATH

I. FULMINATING ANOXIA*

H. G. Swann and Marshall Brucer† ‡

The main cardiorespiratory changes during the process of death have been widely studied. Although usually only one physiological system has been investigated at a time, *e.g.*, the heart (Wiggers, 1941), in carbon monoxide poisoning (Yant, Chornyak, Schrenk, Patty, and Sayers, 1934; Von Oettingen, Donahue, Valaer, and Miller, 1941) and in exsanguination (Negovski, 1945–1946), simultaneous measurements of the main changes in the heart, the breathing and the blood chemistry have recently been made. In these types of fatal anoxia, therefore (we shall employ the term "anoxia," following Peters and Van Slyke (1932) and Van Liere (1942), to mean oxygen want of tissues, regardless of degree and regardless of cause), it is possible to relate the terminal changes in, say, the breathing to the changes in the blood oxygen or the heart. However, such simultaneous measurements are lacking for other types of fatal anoxia: there is none for the simple anoxia consequent to breathing gas mixtures low in oxygen or for the anoxia consequent to obstructive asphyxia. Also a large gap in our knowledge lies in the fact that the great majority of studies of death have been made on anesthetized preparations. General anesthesia not only depresses the cortex; it produces in and of itself anoxia (Marshall and Rosenfield, 1936; Shaw, Steele, and Lamb, 1937; McClure, Hartman, Schnedorf, and

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*From the Carter Physiological Laboratory, The University of Texas Medical Branch, Galveston. These papers report a portion of the results obtained in a program of research into the efficacy of resuscitating procedures. The program is sponsored by the Air Materiel Command, Wright Field, Ohio, under contract No. W 33–038 ac–14379. The co-operation of the Aero Medical Laboratory, Wright Field, is gratefully acknowledged. Received for publication June 1, 1949.

†Now at the Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee.

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Schelling, 1939; Gellhorn, 1943); it depresses the respiration (Robbins, 1935, 1936; McClure, Hartman, Schnedorf, and Schelling, 1939; Gellhorn, 1943; Allen, Echols, Hoeflich, O'Neal, and Slocum, 1947); it alters the cardiovascular reflexes (Wiggers, 1923, 1942; Robbins, Fitzhugh, and Baxter, 1939; Gellhorn, 1943; Allen, Echols, Hoeflich, O'Neal, and Slocum, 1947); it causes a strong acidosis (Leake, Leake and Koehler, 1923; Van Slyke, Austin, and Cullen, 1922); and it alters splenic physiology (Hausner, 1938; Wiggers, 1942). Since all of these systems are intimately involved in the reactions of the organism to anoxia, if we are to have a true picture of anoxic death, the process should be studied without general anesthesia. The difficulty is, of course, that general anesthesia is essential to many types of experimental work. But since the fatal anoxic accidents occur not to anesthetized but to unanesthetized persons, the study of these accidents should be made if possible without the depressing effects of general anesthetics. The comprehensive study of Yant, Chornyak, Schrenk, Patty, and Sayers (1934) on CO-poisoning is of great value because among other reasons, none but local anesthesia was employed; but because the equally comprehensive study of Negovski (1945–1946) on exsanguination was made employing ether and opium as anesthetics, his data are felt to be limited in application, particularly the data on respiration.

In the present study, the terminal cardiorespiratory and chemical changes in several types of overwhelming fatal anoxia have been investigated in dogs.* The types of anoxic death investigated were: obstructive asphyxia, exsanguination, drowning, carbon monoxide poisoning and the deaths consequent to breathing gas mixtures low in oxygen, *i.e.*, while breathing nitrogen, while breathing 2.43 per cent oxygen in nitrogen and while rebreathing through soda lime. During these accidents, in order to obtain a comprehensive survey of the process of death, simultaneous measurements were made

*A preliminary report, of limited distribution, has been presented (Swann, 1948). The data there presented have been amplified and corrected in minor details for these reports. No material changes have been made with one exception: the blood pHs first reported have been corrected from the pH as measured at room temperature to the pH of 38°.

of systolic and diastolic arterial blood pressure, venous pressure in the inferior vena cava, heart rate, heart sounds, electrocardiograms, intrathoracic pressure, pulmonary ventilation, respiratory rate, blood acidity, blood oxygen, blood carbon dioxide, blood lactic acid, plasm proteins, and hemoglobin.

In the first experiments, the terminal cardiorespiratory events of dogs breathing nitrogen gas were measured. This method of producing anoxia is frequently used in experimental studies, although in everyday life it is not often encountered. Inhalation of any inert gas, such as hydrogen or methane produces similar effects. (The "Fire damp" of mines is a mixture of N_2 and CO_2 and so cannot be considered equivalent to breathing pure N_2.) If an aviator is suddenly deprived of his oxygen supply when flying at 35,000 feet and upwards, his behavior is probably similar to that of a man breathing pure N_2 (Armstrong, 1939). This method of producing anoxia was investigated in animals under the general anesthetic, sodium pentobarbital. It was also investigated in animals under local but not general anesthetics, as were all of the other types of anoxia discussed below. In describing these experiments, we shall refer to the dogs as being "unanesthetized." This is to be taken as meaning that the dogs were under local but not general anesthesia. Pain to the animals was prevented by extensive use of the local anesthetic procaine.

In the following reports, we will present the basic data collected, but we shall not attempt a complete analysis and discussion of the experiments. Rather, with the data from all types of anoxia before us, we will attempt in subsequent papers a comparative study of the main physiological changes during the process of anoxic death. Thus the breathing or breathing movements during these different types of death will be described in greater detail in other papers, with an analysis of the chemical and cardiovascular influences on the breathing. Similarly, the changes in electrocardiograms will be compared in still another paper for all the types of death studied.

Methods

1. *Equipment for measuring breathing.* A special metal face mask for the dogs was designed in the shape of a truncated cone. In the middle portion of the cone there was fastened a sheet-rubber diaphragm with a one-inch hole in it; at the base of the cone was inserted another diaphragm with a two- or three-inch hole in it. The dog's muzzle was inserted through the holes of both diaphragms, the first sealing around the muzzle and the second sealing around the head. All air movement was thus directed in and out of the small end of the mask. As an added precaution against leakage, a bandage of rubber sheeting was wrapped around the junction of the dog's head and the mask. The inspired gas was contained in Douglas bags; the expired gas was directed into a recording spirometer, the direction of the flow being controlled by flutter valves. The recording spirometer had a water-sealed bell of 10 L. capacity, the movements of which were recorded on a revolving drum. Thus, both respiratory rate and pulmonary ventilation were measured. Because the respiration of dogs changes rapidly, in these reports the breathing over each 15 second period will be reported, rather than over one minute as is customary with studies on man.

Since in this experiment, a comparison of the dog's breathing patterns will be made, and since also the dogs varied in weight (from 5.5 to 11.8 Kg.) it was necessary to express the breathing in comparable units. To this end, the pulmonary ventilation data will be presented in both its raw form and following in part Gray (1945), in the form of a ventilation ratio, the latter being defined as the ratio of the observed ventilation to the resting ventilation. The resting ventilation (RV) in liters per 15 sec., was calculated from the equation,

$$RV = 0.06308\ W^{.75}$$

the weight (W) being expressed in kilograms. In quiet, well-trained dogs, we have observed pulmonary ventilations of about this magnitude; it is also equivalent to a resting ventilation of 6 liters per minute in a 68 Kg. man. We are therefore confident that it represents a good "basal" figure for the dog.

The "pure" nitrogen gas used in these experiments contained 0.19 per cent O_2.

2. *Blood pressure equipment.* The arterial blood pressure was recorded optically with a water-filled glass Bourdon tube as the pressure-sensitive element (Kubicek, Sedgwick, and Visscher, 1941). The Bourdon tube was connected to the cannula with 41 cm. of "Tygon" tubing. This system had a natural frequency of 64 vibrations per sec.; it recorded diastolic pressures equal to, but systolic pressures about 10 mm. Hg lower than the pressures recorded while using connections of lead tubing rather than "Tygon" tubing. With large pulse pressures, the recorded pressures, using "Tygon" tubing, were 20 mm. Hg lower than those recorded while using lead tubing. Systolic pressures reported in this paper, then are 10–20 mm. Hg lower than we would have obtained, had we used lead tubing in our measuring device.

In the unanesthetized dog, the blood pressure fluctuates much more violently than it does in anesthetized dogs. Figure 1 shows a typical segment of record. It indicates the sort of recording which it was necessary to quantitate: within 2 sec., *nota bene*, the systolic pressure fluctuated with respiratory movements between 235 and 302 mm. Hg and the diastolic between 43 and 136 mm. When confronted with this sort of rapid variation, we have chosen to take the general average of the pressures at the given time; Figure 1 indicates the method. Pulse rates were taken from these records, or, in a few instances where arterial pulsations were so faint as to be imperceptible, from the venous pulsations or from the electrocardiograms.

To measure venous pressure, a catheter (Balfour tubing, O.D. 7/64″) was inserted into a femoral vein; the catheter was then pushed toward the heart until its tip lay in the inferior vena cava about 3 cm. above the diaphragm. At autopsy, the position of the tip was determined accurately. The venous pressures were recorded optically with a sensitive glass Bourdon tube of the same type as described above. In these papers the "effective venous pressure" is defined (Henderson and Barringer, 1913) as the difference between the inferior vena cava pressure and the intrathoracic pressure

(effective venous pressure equals the algebraic sum of venous pressure and intrathoracic pressure). Both were measured at the end of diastole and during an expiratory movement when the intrathoracic pressure curve was relatively flat (Wiggers, Levy, and Graham, 1947).

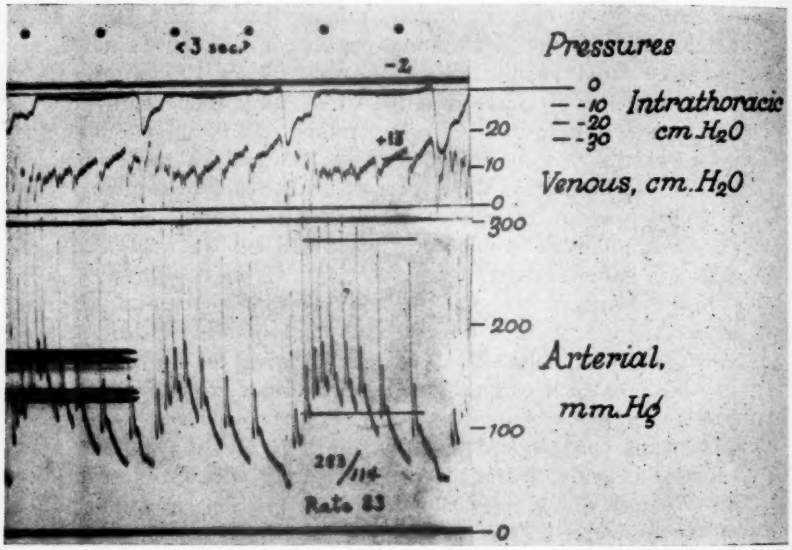

FIGURE 1

Recording of arterial blood pressure, venous pressure, and intrathoracic pressure.

3. *Miscellaneous equipment.* Electrocardiograms (Lead II) and heart sounds were recorded on a Sanborn "Stethocardiette." The intrathoracic pressure was recorded optically, using a third glass Bourdon tube as the pressure-sensitive element. Figure 1 shows the simultaneous recording of arterial blood pressure, venous pressure, and intrathoracic pressure. Measurements of the three pressures are indicated.

4. *Blood chemistry.* At various intervals during the course of the experiments an 8 ml. arterial blood sample was drawn under oil. Potassium fluoride was added as coagulant and then the blood was put under oil in a glass container. The container

was kept immersed in ice water until ready for analysis, all analyses being completed within 6 hours after the start of the experiment. The whole blood samples were analyzed thus:

a. *Oxygen and carbon dioxide* content of whole arterial blood, in duplicate, by the manometric method of Van Slyke and Neill (1924).

The oxygen capacity was computed on the assumption that each gram of hemoglobin carries 1.36 cc. of O_2. The ratio of the observed O_2-content to the O_2-capacity times 100 was then taken as the per cent O_2-saturation. A scrutiny of the tables below will show the unsatisfactory character of this measurement in some instances, *e.g.*, in dog No. I (Table I) at zero time, the measured blood hemoglobin was 11.8 gm. per cent, giving an oxygen capacity of 16.1 vols. per cent. But the measured O_2-content at this time was 19.4 vols. per cent. This is a palpably false result: one of the two measurements must be wrong. Probably in this dog the O_2-capacity was nearer 1.64 cc. per gram of hemoglobin. But in any case, since the dogs' hemoglobin contents fluctuated in all experiments so unpredictably and since the O_2-capacity of the hemoglobin apparently varies in anoxia (Cordier, 1938), in order to have obtained an accurate measurement of O_2-saturation we would have had to measure the O_2-capacities of each sample drawn. We did not attempt this task, but instead have used the method described, even though it does in some instances lead to false conclusions. In any case in which the O_2-content exceeded the computed O_2-capacity, we have arbitrarily taken the saturation to be 100 per cent.

The CO_2-tension was computed as follows: from the blood hemoglobin, the oxygen capacity was computed, assuming that each gram of hemoglobin carried 1.36 cc. O_2. Assuming that the blood was entirely reduced, by using the oxygen capacity (in per cent) and the whole blood pH, the whole blood CO_2-content was converted to serum CO_2-content. Then the pCO_2 and bicarbonate content ($BHCO_3$), using the whole blood pH, were computed. In all instances the methods of Van Slyke and Sendroy (1928) were used.

b. *pH* with a glass electrode ("Electron-Ray pH Meter" of Cambridge Instrument Co.). The pH was determined at

TABLE I

Pure Nitrogen, Nembutalized
Adult Female, 9.8 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg (Systolic / Diastolic)	Pulse pressure, mm. Hg	Venous pressure, cm. H_2O
0	.20	.6	4	19.4	100	40.0	53	18	*	7.15	11.8	6.2	180	140/92	48	—1
1	.85	2.4	7	6.5	42	45.4	49	21		7.25	11.5	6.3	180	147/79	68	—2
2	.35	1.0	7	1.7	10	44.4	42	21		7.31	12.0	6.5	144	154/88	66	3
3	0	0	0	2.3	11	44.8	58	21		7.18	15.3	6.6	119	197/93	104	15
4	0	0	0	3.9	18	48.1	67	23		7.15	16.3	6.6	100	125/42	83	13
5	0	0	0										82	41/22	19	13
6	0	0	0										87	9/7	2	8
7	0	0	0										25	7/3	4	4

*In all of the following tables, a blank space indicates that no adequate records of the given variable were obtained.

room temperature; each observation was converted to the pH of 38° by means of Rosenthal's (1948) formula:

$$pH_{38°} = pH_t - (38 - t)\ 0.0147.$$

c. *Lactic acid* of whole blood in duplicate by the method of Mendel and Goldscheider (1925). In our hands, this method was satisfactory only for gross changes; the values reported here are correct only to the nearest 30 mgm. per cent.

d. *Chloride* of whole blood in duplicate, by the method of Whitehorn (1921).

e. The *densities of whole blood* and *of plasma* in duplicate, by the falling drop method of Barbour and Hamilton (1926). From these densities, employing the nomogram of Phillips, Van Slyke, Dole, Emerson, Hamilton, and Archibald (1943), the plasma proteins and hemoglobin were deduced. Some hemoglobin estimations were checked photocolorimetrically and showed little variation from densiometric measures, even under extreme conditions of hemolysis, hemoconcentration and hemodilution. The hematocrit may also be deduced from the two measures, but we have preferred not to use it, relying instead on the hemoglobin content of the blood.

5. *Preparation of dog.* Healthy adult or young adult dogs, about 8 Kg. in weight, of either sex, were used in our experiments. Under local novocain anesthesia both femoral arteries were exposed; into one was tied a cannula filled with heparin for blood pressure measurement and into the other was inserted an 18-gauge Lindeman transfusion needle with a smooth ream inside it. When a blood sample was to be drawn, the ream was removed, the blood allowed to flow briefly and then an oiled syringe inserted and blood allowed to flow into it. When the blood pressure was very low, as in most of the samples drawn at the end of the experiments, the plunger of the syringe was drawn out in order to obtain the 8 ml. required.

The vein catheter was inserted, as described above, in the femoral vein. The intrathoracic cannula (a small brass tube with a blunt perforated tip) was inserted, also under local novocain anesthesia, between the ribs just below the left axilla. Needles were used for electrocardiographic electrodes, these being inserted subcutaneously, under local anesthesia, in the

right foreleg and left thigh. These preparations consumed about 45 min.

One minute before subjecting the dog to the experiment, a control blood sample was drawn and all recording started. (It is the data obtained at this time which is listed in all the tables as having been taken at "zero" time.) Then the Douglas bag containing the special gas mixture was connected to the valve system and the experiment commenced. The special technics used in obstructive asphyxia, drowning, and exsanguination will be described in the papers so titled.

Complete results were obtained on at least four dogs in each type of overwhelming fatal accident.

Results

A. *Pure nitrogen, nembutalized.* The dose of nembutal (sodium pentobarbital) was "standardized" as suggested by Wiggers (1942), *i.e.*, just enough to abolish pain reflexes but not enough to depress the respiration. The results of four experiments are shown in Tables I, II, III, and IV. A graph of the results on one dog—No. IV—is shown in Figure 2. (The dogs will be referred to by their table number.)

The pattern of respiratory change in dogs while breathing pure N_2 has been described by one of us previously (Swann, Wilson, and Barry, 1945) as follows: "In general terms, the pulmonary ventilation continued good for about 100 sec. with the breathing regular and well co-ordinated; this period we have termed the 'period of eupnea.' Then the breathing became irregular and poorly co-ordinated." This period is essentially a period of gasps; it is unpredictable and sometimes absent. We shall call it the "period of gasping." It lasts from 0 to 3 min.

The four dogs under consideration showed the same pattern of behavior as reported previously. In the period of eupnea there was first a sharp increase in pulmonary ventilation and rate and then a sharp decrease. The period of gasping did not appear in 2 of the 4 dogs.

Arterial blood O_2 decreased sharply over the first minute and fell to about 2 vols. per cent by 2 min. The CO_2-content of whole blood did not change greatly through the whole experiment in any of the dogs. However, the CO_2-tension

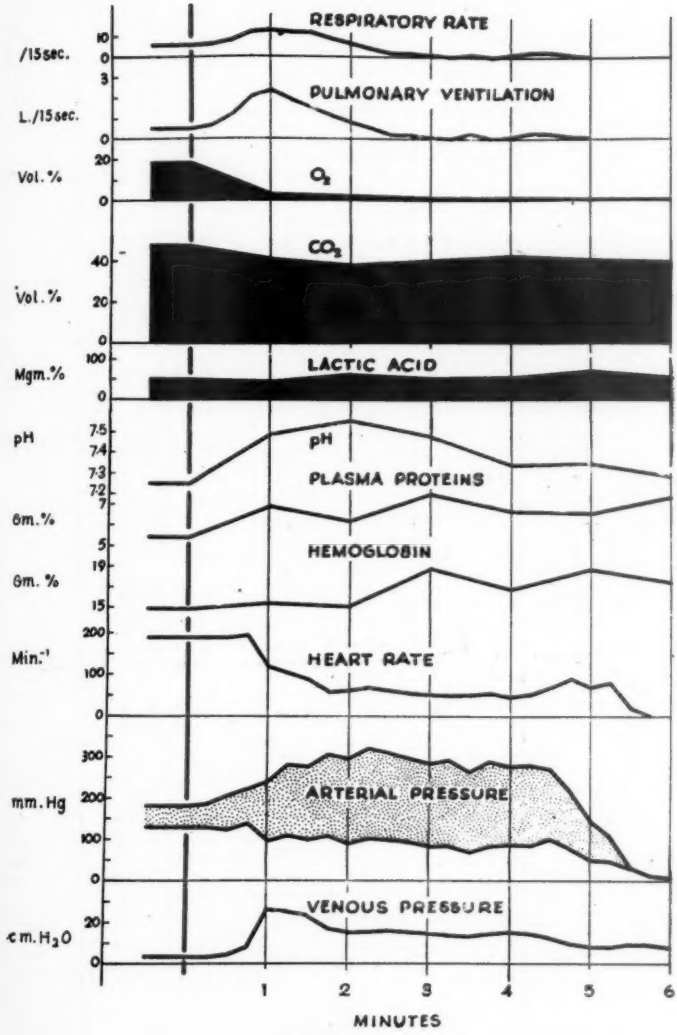

FIGURE 2

Course of fulminating anoxia, nembutalized. Dog No. IV.

TABLE II

Pure Nitrogen, Nembutalized
Young Adult Female, 6.0 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Venous pressure, cm. H_2O
0	.15	.6	3	12.9	71	47.8	75	22		7.09	13.3	6.2	208	136	101	35	3
1	1.0	4.1	11	1.7	14	45.9	46	21		7.28	11.3	6.2	178	146	79	67	7
2	0	0	0	1.5	10	45.9	55	21		7.20	11.4	6.9	95	186	49	137	14
3	.11	.5	1	1.5	10	45.3	65	21		7.12	11.3	6.9	42	158	23	135	13
4	0	0	0	1.9	10	44.6	79	21		7.04	14.6	7.0	118	55	22	33	11
5	0	0	0										150	10	10	0	12

TABLE III

Pure Nitrogen, Nembutalized
Adult Female, 7.0 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Venous pressure, cm. H_2O
0	.05	.2	2	11.7	57	44.5	51	21	0	7.24	15.2	6.1	130	141	93	47	6
1	.63	2.5	8	5.8	27	43.6	38	21	22	7.37	15.8	5.8	138	165	60	105	14
2	0	0	0	2.1	12	45.1	45	21	82	7.30	13.0	5.1	37	223	50	173	23
3	0	0	0	1.4	9	44.5	51	21	35	7.23	11.7	5.7	40	259	44	215	21
4	0	0	0	1.8	12	44.2	67	20	72	7.09	11.0	5.8	130	60	27	33	16
5	0	0	0	0.5	3	43.1	70	20	75	7.07	13.1	5.7	90	17	17	0	18
6	0	0	0										0	10	10	0	15

TABLE IV

Pure Nitrogen, Nembutalized
Adult Male, 7.0 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	Arterial $BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Venous pressure, cm. H_2O
0	.54	2.0	5.5	18.3	90	47.5	50	22	50	7.27	14.8	5.4	190	182	128	54	3
1	2.35	8.6	13	3.2	15	41.3	27	21	45	7.51	15.4	6.9	120	239	98	141	26
2	.80	2.9	6.5	2.3	11	38.3	22	20	62	7.58	15.1	6.2	62	296	90	206	15
3	.08	.3	1	1.7	7	40.3	29	22	52	7.50	18.8	7.5	52	286	85	201	15
4	.08	.3	1	1.4	6	42.6	39	21	55	7.36	16.8	6.7	46	278	89	189	15
5	0	0	0	0.6	2	40.5	37	21	70	7.37	18.8	6.6	70	147	51	96	8
6	0	0	0	0.9	4	39.5	49	19	55	7.21	17.5	7.4	*	—/5		0	8

*Ventricular Fibrillation at 5:31.

first fell rapidly and then commenced rapidly to rise with the onset of apnea. The pH, after an early rise, fell sharply as the CO_2-tension increased.

The heart rate decreased over the first few minutes. The familiar rise of blood pressure in anoxia was found to be primarily a pronounced rise in the systolic component. The diastolic pressure usually fell; it did not rise. Very large pulse pressures, then, were evident. The venous pressure (effective venous pressures were not measured in this experiment) tended to rise when the heart slowed and continued elevated until death. The systemic arterial pressure fell to about zero at 4½–5½ min. Terminally, the decline in systolic pressure was very steep; it fell 150 mm. Hg in about a minute. Circulatory failures occurred 3–4 min. after the blood oxygen was approaching zero and 3–4 min. after eupneic breathing had ceased.

The electrocardiographic changes were as follows: the P waves tended to drop out or dissociate from the QRS complexes from the first to the third min. They then usually reappeared. The R waves decreased and the T waves meanwhile increased in amplitude. During the systemic pressure collapse, the ST segments showed a high take-off and slurred upward into a high peaked T. Following collapse, the ST segments were elevated higher and higher until the R and T waves were fused into a single monophasic complex. The dog No. IV, ventricular fibrillation occurred at 5 min., 31 sec. when the blood pressure was 70/35. This reverted after 2½ min. to flurries of monophasic R and T waves. The last discernible complexes were observed at 20–26 min.

The first heart sound disappeared when the blood pressure reached about 50/20. The second sound disappeared about 20 sec. before the first.

B. *Pure nitrogen* (local anesthesia only). The results of four experiments are shown in Tables V, VI, VII, and VIII. A graph of the events in dog No. VII is shown in Figure 3.

Regular breathing—the period of eupnea—had ceased in these four dogs by 2 min. after the start. A brief period of gasping was shown by each of them at about 3 min. The CO_2-content fell during the first min. about 5 vols. per cent and subsequently remained stationary. The pH, after an

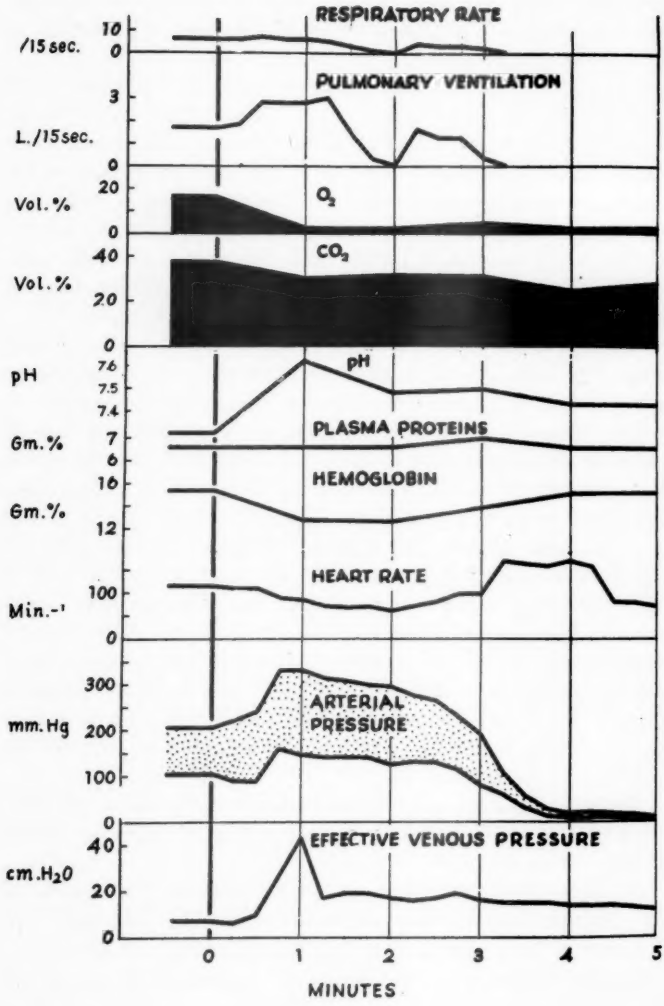

FIGURE 3

Course of fulminating anoxia. Dog No. VII.

TABLE V

Pure Nitrogen
Young Adult Male, 8.0 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.50	1.7	5	17.8	94	40.6	35	20	10	7.38	13.9	7.0	73	181	109	72	18	0
1	.03	.1	1	1.6	8	40.2	26	21	10	7.52		6.5	69	286	137	149	14	0
2	0	0	0	3.6	19	52.3	39	27	23	7.45	14.0	6.5	125	234	145	89	10	0
3	.65	2.2	4	1.2	6	39.4	34	20	33	7.38	14.2	6.4	120	204	102	102	13	0
4	0	0	0	0.7	5	38.9	43	18	54	7.24	11.2	6.6	187	52	20	32	10	0
5	0	0	0	0.5	3	39.7	48	19	59	7.20	11.0	6.8	90	11	0	11	11	0
6	0	0	0	0.5	3	38.6	42	16	46	7.25	13.2	5.2	35	2	0	2	11	0

TABLE VI

Pure Nitrogen
Young Adult Female, 8.2 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic / Diastolic	Pulse pressure, mm. Hg	Venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.78	2.5	4	20.2	96	39.2	40	19	10	7.29	14.4	6.8	125	214/98	116	19	
1	1.26	4.1	6	1.6	8	33.9	18	18	10	7.61	15.5	6.2	62	358/124	234	57	
2	0	0	0	3.0	15	34.1	21	16	10	7.54	14.5	6.7	58	354/138	187	33	
3	.81	2.6	4	2.6	12	32.7	25	17	21	7.45	15.4	6.7	102	294/132	128	28	
4	0	0	0	0.7	4	36.0	34	18	57	7.34	14.8	6.7	146	111/50	61	27	
5	0	0	0	1.5	8	29.7	29	14	54	7.31	14.2	6.8	102	16/2	14	29	
6	0	0	0	1.0	5	34.8	37	17	47	7.28	14.8	6.8	35	2/2	0	24	

TABLE VII

Pure Nitrogen

Young Adult Male, 9.5 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	1.70	4.9	6	16.8	83	37.4	38	18		7.30	15.4	6.6	115	205	104	101	7	—2
1	2.80	8.0	6	2.4	14	30.3	16	16		7.62	12.8	6.6	85	333	146	187	43	12
2	0	0	0	2.4	14	31.6	21	15		7.48	12.7	6.6	62	296	125	171	17	—3
3	.37	1.0	2	4.8	25	31.2	21	16		7.50		7.0	98	192	80	112	16	—3
4	0	0	0	2.4	12	24.8	19	13		7.43	15.2	6.6	170	19	9	10	14	—3
5	0	0	0	3.0	15	28.2	21	14		7.43	15.3	6.6	72	5	3	3	12	—2

TABLE VIII

Pure Nitrogen

Adult Male, 8 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.63	1.8	4	18.6	97	31.1	34	15	0	7.26	14.1	6.5	71	216	109	107	—1	—6
1	.35	1.0	3	3.0	16	27.8	17	15	0	7.56		6.5	71	334	102	232	—10	—28
2	0	0	0	5.6	29	29.7	27	15	30	7.35	14.1	6.6	78	326	96	230	6	—10
3	.68	1.9	2	1.4	7	26.7	27	13	62	7.30			102	223	80	148	9	—8
4	0	0	0	1.2	6	27.1	30	13	110	7.26	14.6	6.7	150	52	16	36	4	—9
5	0	0	0										58	8	8	0	3	—8

initial sharp rise, decreased quickly to normal or acidemic levels. Meanwhile, the pCO_2, after the initial sharp fall, rose until at death it was only slightly subnormal. Accompanying the terminal rise in pCO_2 was a rise in lactic acid and a fall in blood bicarbonate.

The heart rates fell sharply at once; they remained low except for a terminal tachycardia, occurring at about 4 min. after the start and at the time when the systolic blood pressure was declining rapidly. A pronounced rise in systolic pressure occurred quickly and then it fell sharply at about 4 min. Early during the anoxia, the diastolic pressure also rose, but then declined sharply as the systolic pressure fell. The systemic pressure failed abruptly 3½–4½ min. after the start, 2–3 min. after regular breathing stopped and ½–1½ min. after gasping ceased.

In the electrocardiograms the P waves became isoelectric early in the experiment (30–90 sec.) when the heart slowed and appeared again at 3–3½ min. with the late tachycardia. The ST junction became elevated at 1¼–1½ min. This elevation began as a slight displacement, and then gradually increased until the QRST almost became one continuous positive deflection. During the period of systolic collapse, which occurred between 3½–4½ min., there were small P waves and low voltage QRS waves; the ST segment was high and slurred into a high peaked T wave. Following collapse, the QRST waves were completely joined in one postive deflection. The last discernible complexes were at 12, 22, and 25 min. in 3 dogs.

The second heart sound disappeared at the beginning of the period of systolic collapse. The first sound disappeared 1–2 min. later.

Discussion

As mentioned above, in this paper the analysis and discussion of these results will be brief and preliminary only, reserving fuller discussion for future papers. For example, it is generally held that anoxia causes cardiac acceleration: "It is well known," states Van Liere (1942), "that acute anoxia produces an acceleration of the heart rate." But in the experiments reported here, there was an *early* acceleration in

only one of 8 dogs (No. III). The acceleration in most dogs appeared late—at about the fourth min.—when the heart was failing. The explanation for this difference between our results and those of others is to be found in the degree of anoxia and the absence of general anesthesia. This will be more fully discussed in the third paper of this series.

Regular breathing in fulminating anoxia stops early, to be followed by a period of very irregular gasping. In the unanesthetized dogs the breathing was more vigorous and the period of eupnea was shorter. Because in this paper the breathing is shown only during the 15 sec. interval exactly on the even minute, omitting three 15 sec. intervals between each reading, the more vigorous breathing of the unanesthetized animals is not apparent. However, the changes in blood gases are best interpreted from this phenomenon: the more vigorous breathing caused the unanesthetized dogs' O_2-content and CO_2-content to fall faster than those of the anesthetized dogs.

The great rapidity of change in the blood gases is noteworthy, particularly in the unanesthetized dogs. Invariably the arterial O_2-content had dropped to 3 or less vols. per cent by one minute. The dogs usually became unconscious about 40 sec. after the start, with clonic and tonic convulsions starting at about this time. The CO_2-content and CO_2-tension rapidly decrease, the latter being roughly halved within the minute.

The changes in acid-base equilibrium (Peters and Van Slyke, 1932; Van Liere, 1942) are a primary CO_2 deficit, which changes rapidly to a primary CO_2 excess during the apnea and is accompanied with a metabolic acidosis. The same changes have been reported in detail recently by Grodins, Lein, and Adler (1946). In the metabolic acidosis, the blood lactate increases in proportion to the blood bicarbonate decrease. This will be further discussed in other papers.

Although the anoxic apnea is not accompanied by a rise in CO_2-content, the effective increase in CO_2 is shown by the pronounced rise in CO_2-tension during the apnea.

It is usually stated that the rapid rise in pH in these circumstances—about 0.3 pH units in the first minute in the unanesthetized dogs—is due to the over-breathing, and it is

called a "respiratory alkalosis." This is only true in part, for Gesell, Krueger, Gorham, and Bernthal (1930) have shown that in dogs subjected to anoxia, with the chest open and the respiration kept constant with a pump, a considerable alkalemia occurs in N_2 anoxia, the pH being found to rise about .2 pH units. This was thought due to the change of all the hemoglobin to the weakly acidic reduced form. It is apparent, then, that the term "respiratory alkalosis" is not strictly correct. The alkalosis is better called a "respiratory and hematic alkalosis."

The blood hemoglobin rose sharply in 3 of the 4 nembutalized dogs at the 3d or 4th min., confirming numerous reports (DeBoer and Carroll, 1924; Barcroft, Murray, Orahovats, Sands, and Weiss, 1925; Hausner, 1938; Jarcho, 1943). This is due to a splenic contraction; it is particularly striking after barbiturate anesthesia which causes a marked previous dilation of the spleen. It also is readily observed in well-trained dogs (Barcroft, 1938; see also Cannon, 1939). In our series of experiments, the only condition in which the reaction was found to occur was in the anesthetized dogs; in all of the other types of anoxia studied by us, in all of which local anesthesia only was employed, a pronounced hemoglobinemia was never observed. This is probably due to the fact that in our untrained dogs, the spleens were maximally contracted because of apprehension over the experimental conditions. Hence little or no further splenic contraction could occur in the animals' "emergency reactions," to the anoxia.

The plasma proteins rose sharply in the anesthetized animals, confirming the results of Calvin (1941), who suggests in explanation a capillary leakage of fluid. However, this change was absent in the unanesthetized dogs, and as in the case of hemoglobin, is absent in all other types of anoxia to be studied. This situation suggests that the spleen may be responsible for the rise of plasma proteins in anoxia of the anesthetized dog.

The very slow pulse rates which we find characteristic of fulminating anoxia became most pronounced at 2–3 min. after the start of inhaling N_2. The slowing always took place just as the period of eupnea was coming to a close. It was accom-

panied with cardiac contractions of great strength, the systolic pressure rising in the unanesthetized dogs to 286–358 mm. Hg. This response to anoxia is the familiar strong sympathetic stimulus, with a superposed cardiac slowing mediated through the vago-sympathetic medullary center (Mathison, 1910; Greene and Gilbert, 1922). The absence of P waves in the ECG is taken as evidence of strong vagal cardiac inhibition (Mathison, 1910) with an idioventricular rhythm. This succession of events—apnea and cardiac slowing—has been called the "cardiorespiratory crisis" (Greene and Gilbert, 1921, 1922; Schneider and Truesdell, 1924; Sands and DeGraff, 1925; Wiggers, 1939).

Electrocardiograph deflections continued for some 20 min. after the death of the dogs, *i.e.*, after the blood pressure declined to zero. This has been observed in man also (Robinson, 1912; and see Negovski, 1946). But we cannot take the disappearance of rhythmic electric changes in the heart as evidence that the organ is dead, for hearts have been revived by special perfusion technics after as long as six hours after "death" (Kountz, 1936).

The second heart sounds always disappeared before the first (ventricular fibrillation excepted) in this experiment and in the others to be reported. This phenomenon has also been reported by Crile and Dolley (1908). It is caused in our opinion by a difference between the forces with which auriculo-ventricular and semilunar valves are "snapped shut": in the failing heart, the stroke volume may be great enough to snap shut the auriculo-ventricular valves and produce a sound. But it may not be great enough to stretch greatly the large-volumed "windkessel." Hence the windkessel, recoiling from stretch, snaps shut the semilunar valves only very weakly—so weakly in fact that no sound is heard. This phenomenon will be further analyzed in another report.

In all these studies on anoxia, including the present one (nembutalized dogs excepted) and those to be reported subsequently, we have measured the effective venous pressure as defined by Henderson and Barringer (1913), with the hope that some information about the venous return to the heart might be gained and that in some instances at least we would

find that the circulatory failure in anoxia, as in shock (Wiggers, 1942; Richards, 1944), could be ascribed to a defective venous return. This in turn could perhaps be ascribed to peripheral vascular failure. But the measurement of effecctive venous pressure was a fruitless one. The only cases in which consistent results were obtained were in the nembutalized dogs breathing N_2, in drowning, and in exsanguination. In all the others, the results were so variable as to defy analysis. For example, in the 4 dogs breathing N_2 while under local anesthesia, as circulatory failure approached, in one dog (No. VII) the effective venous pressure was high but in another (No. VIII) it was low. But the cardiac behavior of the two dogs was very much the same.

The measurement is a difficult one, as two recent studies show (Brookhart and Boyd, 1947; Wiggers, Levy, and Graham, 1947). Also a glance at Figure 1 will indicate how severe a task it is to appraise the violent fluctuations in intrathoracic and great vein pressures. Because of its fruitless nature, we shall not, in general, discuss this measurement any further in these papers. The occcasional very high values given, *e.g.*, 43 cm. H_2O in dog No. VIII at 1 min., were due to the dog's struggles or convulsions when the measurement was being taken.

The important question as to whether the terminal decline in systemic arterial blood pressure in uncomplicated anoxic death is caused by myocardial failure or a peripheral vascular failure has not been settled in our experiments. Although we shall sometimes say "the heart failed as a pump" or, as in the second paragraph above, "heart failure approached," such phrases are not to be taken to mean that the point is proved. The phrasing is used for the sake of simplicity in the argument; what is actually meant by it is that the systemic arterial pressure was rapidly declining or was, essentially, at zero.

Summary

Simultaneous measurements were made of the breathing, systolic and diastolic blood pressure, effective venous pressure, electrocardiograms, heart sounds, blood gases, pH, lactic acid, hemoglobin and plasma proteins in dogs during the anoxic

death caused by breathing pure nitrogen. Results on nembutalized dogs and on dogs under local anesthesia confirm those reported by previous observers. Anoxic death from pure nitrogen is a complex process involving serial failure of many vital activities.

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THE CARDIORESPIRATORY AND BIOCHEMICAL EVENTS DURING RAPID ANOXIC DEATH

II. ACUTE ANOXIA*

H. G. Swann and Marshall Brucer

When flyers are suddenly deprived of their oxygen supply at altitudes of 25,000–35,000 feet above sea level, death probably occurs in from 5 to 40 minutes (Swann, 1946). This type of anoxic death is less fulminating than the anoxia of breathing pure nitrogen, and therefore a special attempt to study it was made. It was found empirically that dogs breathing 2.43 per cent oxygen in 97.57 per cent nitrogen (at sea level) survive from 3.7 to 42 min. (Swann, Wilson, and Barry, 1945), and consequently this gas mixture was selected for use. Actually the mixture is equivalent to an altitude of about 40,000 feet, where man survives only 3–5 min. Dogs, being very resistant to anoxia (McDonough, 1939; Stacy, Whitehorn, and Hitchcock, 1948), survive from 4 to 29 min. of exposure to this altitude when it is simulated in a decompression chamber (Swann, Wilson, and Barry, 1945).

Methods

The methods used are described in the previous paper. The experimental work was done employing local anesthesia only. The gas mixture was prepared by mixing known quantities of nitrogen and air in a spirometer. Since the N_2 gas employed varied in its contamination with O_2, its O_2-content was ascertained by the Haldane gasometric procedure and then the N_2 was diluted with enough air to bring it to 2.43 per cent O_2.

Results

The results are shown for 4 dogs in Tables I, II, III, and IV, with a graph of the changes in one dog in Figure 1.

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*From the Carter Physiological Laboratory, The University of Texas Medical Branch, Galveston. This paper reports a portion of the results obtained in a program of research on the efficacy of resuscitation procedures. The program is sponsored by the Air Materiel Command, Wright Field, Ohio, under contract No. W 33–038 ac–14379. Received for publication June 15. 1949.

TABLE I

2.43% Oxygen in Nitrogen
Adult Female, 7.5 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.55	1.9	6	19.4	97	40.6	42	19	0	7.28	14.8	7.1	82	247	133	114	—5	—8
1	1.80	6.2	9.5	4.3	21	36.1	24	18	40	7.50	14.8	7.1	205	300	128	172	—5	—9
2	1.80	6.2	9.5	3.9	19	30.7	20	16	0	7.52	15.3	6.7	68	285	105	180	—5	—19
5	2.15	7.4	11	4.6	21	21.2	15	11	94	7.49	16.3	6.6	68	270	115	155	—5	—14
9	1.90	6.6	8.5	3.7	17	13.2	12	7	121	7.36	16.3	7.1	80	276	111	165	—1	—12
12	1.30	4.5	6.5	2.5	11	9.6	13	5	194	7.16	16.0	7.1	84	160	62	98		
13	.80	2.7	3.5	3.1	15	8.4	12	4	167	7.15	15.8	7.1	70	169	50	119		
14	.60	2.1	2.5	3.0	14	12.5	18	6	230	7.12			72	216	50	166	3	—3
15	1.40	4.8	3	2.3	11	14.7	26	7	194	7.04	15.3	7.0	110	60	15	45	6	—2
16	0	0	0										30	8	8	0	6	—2

TABLE II

2.43% Oxygen in Nitrogen
Adult Female, 9.0 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.35	1.2	2	18.8	88	43.1	43	21	0	7.32	15.9	6.7	120	217	89	128		
1	2.85	9.5	7	10.1	47	43.8	35	24		7.46	15.9	6.6	150	340	168	172		
2	2.10	7.0	9	4.9	22	36.7	24	19	0	7.51	16.2	6.7	64	376	96	280	9	—9
5	.57	1.9	3	4.5	21	28.4	19	15	57	7.51	15.8	6.6	84	269	124	145	10	0
11	.63	2.1	3	7.1	33	25.2	22	12	82	7.37	15.8	6.6	56	352	104	248	12	—3
14	.38	1.3	5	7.1	29	25.5	30	13	95	7.24	17.7	6.7	56	336	108	228	11	—4
15	.34	1.1	5	2.6	12	18.3	27	9		7.14	15.8	7.7	40	320	46	274	16	—2
18	0	0	0	2.6	12	13.4	23	6	87	7.06	16.3	7.1	56	262	55	207	16	0
19	.11	.3	1	2.8	12	16.5	33	8	96	6.98	16.9	7.1	60	208	32	176	13	—1
20	0	0	0	3.0	13	17.1	38	8	108	6.93	17.2	7.6	150	25	9	16	12	—1
21	0	0	0										60	10	4	6	9	—3

TABLE III

2.43% Oxygen in Nitrogen
Adult Female, 6.1 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.47	1.9	4	23.0	96	49.3	45	24	0	7.36	17.6	6.6	160	230	125	105	14	0
1	2.25	9.0	5.5	8.0	37	44.9	25	24	0	7.60	16.0	7.0	142	305	146	159	22	7
2	1.95	7.6	7.5	5.8	22	40.6	24	22	60	7.58	19.4	6.9	147	337	194	143	22	—4
5	1.45	5.8	6	3.6	13	27.0	19	14	85	7.50	20.0	6.9	135	287	164	123	9	—4
6	1.00	4.0	4.5	3.0	12	22.8	18	12	100	7.44	18.6	6.9	120	292	146	146	13	—4
9	.57	2.6	3	2.2	8	17.7	16	9	195	7.38	19.5	6.9	118	280	132	148	15	—5
10	0	0	0										*	—	/9	0	18	—6
11	0	0	0	2.1	8	16.2	14	9	190	7.41	19.0	8.5						

*Ventricular fibrillation at 9:36.

TABLE IV

2.43% Oxygen in Nitrogen
Young Adult Male, 7.0 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.32	1.2	4	14.3	92	48.2	46	22	0	7.30	11.5	6.3	81	210/100		110	—2	—4
1	2.37	8.8	10	4.9	23	14.7	8	8	0	7.60	15.9	6.5	100	364/156		208	118	56
5	.26	1.0	1.5	1.9	11	30.8	24	15	85	7.41	13.2	6.5	150	282/142		140	13	—1
6	0	0	0	2.1	10	29.6	25	15	95	7.39	15.4	6.5	82	247/80		167	15	—2
7	.13	.5	3	2.6	15	27.7	24	13	140	7.36	12.9	6.7	138	106/40		66	13	—2
8	0	0	0	2.9	17	23.9	24	12	130	7.30	12.8	6.5	111	23/9		14	10	—2
9	0	0	0										98	6/6		0	11	—2

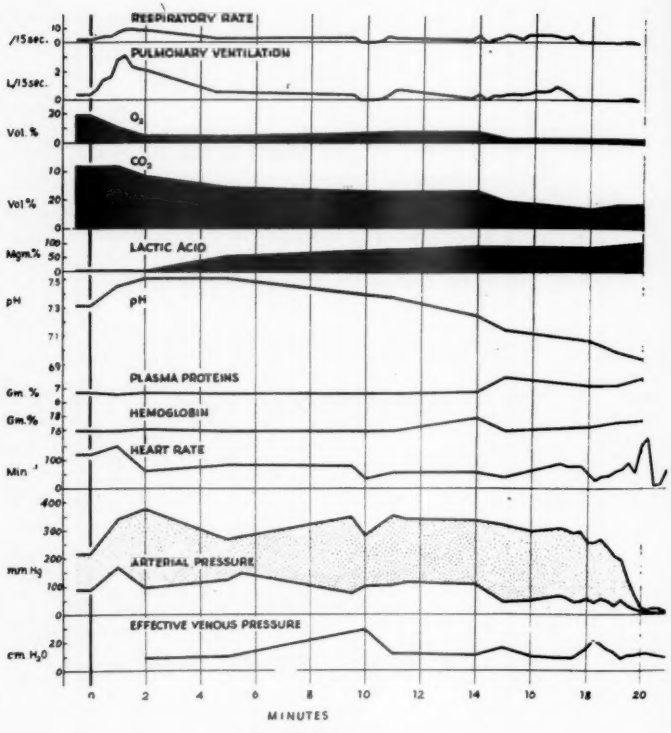

FIGURE 1

Course of acute anoxia. Dog No. II.

The breathing was at once strongly stimulated by the anoxia to about eight times the resting ventilation. Although in this paper the minute-to-minute changes are not given, they resemble, in general, the changes shown in Figure 1: a very strong stimulation for 4–8 min., but then a decrease to a lower level which was well sustained until heart failure. The breathing cannot be said to have become weak or shallow at any time; it did not "taper off" just before death. Rather it remained at a level equal to the resting ventilation or higher, until abruptly it ceased. These results confirm the recent report of Chambers, Brewer, Davenport, and Goldschmidt (1947) on

the breathing of dogs in anoxia. In 2 of our 4 dogs, no period of gasping, as described previously (Swann and Brucer, 1949a), occurred. In all dogs, breathing ceased either as the circulation was failing or 1–2 min. beforehand.

The arterial blood O_2-saturation fell to about 22 per cent within 2 min. at most from the start and tended to remain at this level for several minutes thereafter. It then slowly dropped to about 12 per cent, with respiratory arrest and cardiac failure occurring some 4 min. later. The CO_2-content and tension fell continuously right from the start, due to the strong hyperventilation that occurred. The rapidity of change is notable: in dog No. IV, for example, after 1 min. of breathing 2.43 per cent O_2, the blood CO_2 dropped from 48 to 15 vols. per cent and the pCO_2 dropped from 46 to 8 mm. Hg. A strong "washing out" of the body's CO_2 is also apparent: in dog No. I, at 13 min., for example, the blood CO_2 had fallen to 8.4 vols. per cent and the blood bicarbonate to 4 mE./L.—the lowest values observed in all the anoxic deaths we have studied. The pH meanwhile rose in a respiratory and hematic (Swann and Brucer, 1949a) alkalosis. However, after about 5 min. the blood lactic acid started to rise and the pH started to fall.

The blood pressure, in both systolic and diastolic components rose sharply just as the dog took its first few breaths of 2.43 per cent O_2 (see Figure 1) and simultaneously the pulse rate rapidly increased. In 2 of the 4 dogs, this was quickly followed by a pronounced bradycardia. With the bradycardia, the diastolic pressure may be low (No. II, *e.g.*) for long periods before the heart actually fails. When the blood pressure declined, the decline was most sharply apparent in the abrupt fall in pulse pressure, for within one minute it dropped from about 160 to 45 mm. Hg or less in all of the dogs. This sudden failure of the circulation took place at 16, 21, 10, and 9 min., respectively, in the 4 dogs. The effective venous pressure was well sustained throughout.

Dog No. III experienced ventricular fibrillation at 9 min., 36 sec; 18 sec. before this point, the blood pressure was 240/130, indicating that the heart was strong until just before ven-

tricular fibrillation supervened. Breathing continued in this dog for 20 sec. after the heart had fibrillated.

In the electrocardiograms the P waves showed a decrease in voltage early; they then disappeared and reappeared, sometimes associated with and sometimes dissociated from the ventricular complexes. In 3 dogs there appeared waves similar to those of auricular fibrillation shortly before systolic collapse. In all cases the P wave disappeared completely before systolic collapse. In 2 dogs, it again reappeared long after systolic collapse.

In all 4 dogs, low voltage in the R wave developed early. The T wave increased in amplitude shortly thereafter and within 3 to 5 min. Inverted Rs with high T waves appeared. During the period of systolic collapse, there were low voltage QRS waves, and high S–T take-offs, fused into low voltage T waves. In 3 dogs following systolic collapse, R waves became upright, ST segments climbed higher and then fused into high T waves to form a single monophasic complex. Dog No. IV showed temporary ventricular fibrillation about 2 min. after heart failure. This soon disappeared, with the QRST waves reappearing as single monophasic complexes. The last complexes appeared in the dogs at 21–28 min., some 10 min. after heart failure.

Discussion

The great variability in period of survival, viz., 16, 21, 10, and 9 min., occurred in the face of our attempts to keep constant the conditions of anoxia. The same variability was noticed in a previous study (Swann, Wilson, and Barry, 1945), in which the period of survival was found to range in a group of 26 dogs from 3.7 to 42 min. A similar variability was found, *i.e.*, survival times ranging from 3.8 to 29 min., in a group of 14 dogs exposed to a simulated altitude of 40,000 feet *(loc. cit.)*. As pointed out in that paper, the variability in survival was not related to weight, sex, age (whether young or adult) or whether the dog was quiet or excited when the experiment started. This great variability in survival has been reported for dogs in other types of fatal anoxia: progressive anoxia (Yant, Chornyak, Schrenk, Patty,

and Sayers, 1934; Swann and Brucer, 1949c), in CO-poisoning (Yant, Chornyak, Schrenk, Patty, and Sayers, 1934; Von Oettingen, Donahue, Valaer, and Miller, 1941; Schwerma, Ivy, Friedman, and LaBrosse, 1948; Swann, 1949a), and in exsanguination (Negovski, 1945–1946). Some explanations of it will be attempted in this and in subsequent papers.

A clue to the variability in this type of anoxia is furnished by the pulse rates of the four dogs: whereas the two surviving the longest time exhibited a strong and early bradycardia, those surviving the less time did not show it. In fact, when the number of heart beats is counted for each dog from the start until the blood pressure had fallen to about 50/15, they total for the 4 dogs, respectively, 1,260, 1,390, 1,260, and 1,050 beats—a surprisingly good correspondence in total number of contractions. It appears therefore that in this type of anoxia, the heart's metabolites will furnish about 1,200 contractions. If these are expended rapidly in tachycardia, the animal dies soon; if slowly, with a pronounced bradycardia, the animal lives long. This assumes that the heart's O_2 consumption is directly related to its rate, an assumption supported by the study of Starling and Visscher (1927). It is also known *(loc. cit.)* that the heart's oxygen consumption is directly related to diastolic size and hence a slow heart rate with large diastolic size would cause a high O_2 consumption *per beat*. The two factors, then work against each other; but in our case, the consumption *per minute* is presumed less for a slow heart than for a rapid heart, and hence the bradycardic dogs survive longer.

An additional factor is the rate of decline of the O_2-saturation, because by and large, dogs dying in a short time reached lower O_2-saturation sooner: at 5 min. their arterial saturation was about 12 per cent, whereas it was 21 per cent in the dogs dying after a longer time. This in turn is thought to be related to the convulsive behavior of the dogs. In a previous paper (Swann, Wilson, and Barry, 1945) this comment was made: "The gross behavior of the dogs which stopped breathing early was different from those which lived longer . . .; the short-lived dogs had early and violent convulsive attacks, with severe episthotonus. . . . The longer-

lived dogs had less violent convulsions; they appeared to pass through the early (convulsive) phase easier." The more violent convulsions would, of course, use up the available metabolites sooner, thus hastening the onset of death.

Recently, two studies of dogs in anoxia (Randall, 1944; Stacy, Whitehorn, and Hitchcock, 1948) have associated greater tolerance to anoxia with the strength of respiratory stimulus which the anoxia induces: the greater the response, the longer the survival. This conclusion was not confirmed by our experiments, for all 4 dogs experienced an early strong respiratory stimulus of about the same magnitude. We suspect that the conclusion holds solidly for anesthetized dogs (morphine and barbitol, and nembutal, respectively, were used in the experiments of Randall, 1944, and Stacy, Whitehorn, and Hitchcock, 1948), but it does not hold for unanesthetized dogs. Our longest survivor (No. II) had, in fact, after the early respiratory stimulation, the lowest pulmonary ventilation in the group. As indicated above, we suspect that this was in part responsible for the dog's long survival.

The data for these 4 dogs prompt the question: is death in this type of anoxia due to respiratory failure or to circulatory failure? In the case of dog No. III, which experienced ventricular fibrillation, death is certainly due primarily to heart failure, for the accident happened while the dog was breathing at good volume and the dog continued breathing for 20 sec. after the heart had failed. In the case of dog No. I, the breathing failed just as the circulation was failing: the last gasp occurred at 15:03 when the blood pressure was 39/19. Furthermore, in this dog, the breathing was strong right up to the end. Hence in this dog also, we conclude that the circulation failed, in substance, before the breathing. In dogs No. II and IV, however, the conclusion is the opposite: in both dogs the breathing stopped definitely about 1 min. bebore the circulation failed.

In a study of a larger series of dogs breathing 2.43 per cent O_2 (Swann, Wilson, and Barry, 1945), the same phenomenon was observed: in 17 of 41 dogs, the breathing failed *after* the pulse became impalpable. The longer the dog survived, the more likely was the circulation to fail before the breathing.

In summary, therefore, in dogs breathing 2.43 per cent O_2, circulatory failure precedes respiratory failure in roughly half the cases. We shall meet with this same phenomenon in CO-poisoning and in exsanguination; it will be discussed further in the papers below (Swann and Brucer, 1949 d and g).

The changes in acid-base equilibrium in this type of anoxic death are, first, a strong primary respiratory and hematic alkalosis and CO_2 deficit. Next, there follows the rapid development of a metabolic acidosis. The data show that the pH starts to decline just as the blood lactic acid starts to rise; the process starts about 5 min. after the onset of anoxia. If the dog dies soon (Nos. III and IV), the pH does not decline greatly, but if the dog survives for a long time, the pH continues to decline, until death in strong acidosis occurs. Meanwhile the alkali reserve decreases as available base is preempted by the strong lactic acid.

Lactic acid certainly plays the major role in this metabolic acidosis. When the blood bicarbonate is plotted against the blood lactic acid, as shown in Figure 2, the effect of lactate on the bicarbonate is apparent. In the graph we have plotted the lactate in milliequivalents; as the trend line indicates, one mE./L. of lactate preempts 0.7 mE. of bicarbonate. Other

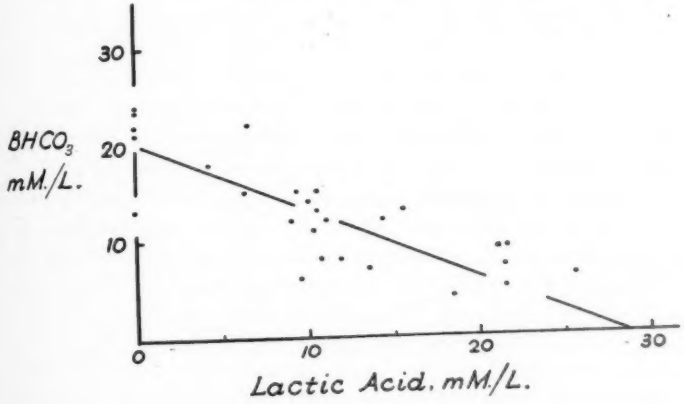

FIGURE 2

Relation of $BHCO_3$ to lactic acid.

bases, in especial strongly reduced hemoglobin, undoubtedly help to neutralize the acid.

The extreme alkalosis and acapnia of our dogs has been described; it goes, in the absence of general anesthesia, confirming Koehler, Behneman, Renell, and Loevenhart (1925), to extremes far beyond those usually discussed in the literature. However, dogs recover readily from this extreme acapnia, for they may be readily resuscitated just when the circulation is finally failing (Swann, 1948, 1949a). For this and other reasons, we cannot agree with Henderson (1938) or Gellhorn (1943) who insist that acapnia is fraught with danger to the animal. It is undoubtedly dangerous, but the anoxia is a much greater danger. Without the hypernea, the arterial saturation might very well be incomplete because the blood is so rapidly circulating through the lungs. Furthermore, the hypernea, causing a decline in the pCO_2 of the alveolar air, allows, as it were, more space for O_2 molecules. In substance, to get the most out of the small amount of O_2 available, the animal must over-breathe tremendously.

But in anoxia, says Haldane (1919), "The body is calling for both O_2 and acid." The hypernea is advantageous in some aspects but it has the disadvantage that it depletes the animal secondarily of the volatile acid, CO_2, which in turn makes the hemoglobin cling to its small complement of O_2 with greater tenacity. To replace, as it were, the lost acid, lactic acid is a fine substitute. And in long-continued acute anoxia, the acidosis goes to great extremes, as shown by both Koehler, Brunquist and Loevenhart (1925) and ourselves. The ideal adjustment to acute anoxia is hypernea and acidosis.

Ventricular fibrillation appeared in 2 of the 4 dogs. On the other hand, it appeared only twice in 111 dogs studied in experiments on resuscitation from breathing 2.43 per cent O_2 (Swann, 1948, 1949a). It is, therefore, a relatively rare event in this type of anoxia. We cannot agree with Resnik (1925) or Wegria (1944) that ventricular fibrillation is common in anoxia; regardless of the type of anoxia, it rarely occurs. This will be amplified in one of the following papers (Swann and Brucer, 1949g).

SUMMARY

Simultaneous measurements were made of breathing, systolic and diastolic blood pressure, effective venous pressure, electrocardiograms, heart sounds, blood gases, pH, lactic acid, hemoglobin, and plasma proteins in dogs, under local anesthesia, during acute anoxic death caused by breathing 2.43 per cent oxygen in nitrogen at sea level.

The great variability in survival is thought to be due in part to the degree of slowing of the heart: the greater the bradycardia, the longer the survival. In this type of anoxia, the breathing frequently fails after circulatory failure. The changes in acid-base equilibrium were found to be first a respiratory and hematic alkalosis and then a superimposed metabolic acidosis, lactic acid being the main metabolic acid involved.

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THE CARDIORESPIRATORY AND BIOCHEMICAL EVENTS DURING RAPID ANOXIC DEATH

III. PROGRESSIVE ANOXIA*

H. G. Swann and Marshall Brucer

Progressive anoxia, that is, a slow progressive decrease in the tissue oxygen tension, is usually studied by causing the subject to rebreathe air in a spirometer through soda lime, thus slowly depleting the inhaled oxygen. Death from this type of anoxia has been studied in greater detail, carbon-monoxide poisoning and exsanguination excepted, than any other type of overwhelming fatal anoxia. The behavior of the cardiovascular and respiratory systems, in especial, has been carefully explored in this type of death, because of the impetus given by World War I to its study and because of the pioneering studies of the Medical Research Laboratory of the (U.S.) Air Service. The studies included investigations on men rebreathing through soda lime (Lutz and Schneider, 1920a and b; Greene and Gilbert, 1920; Schneider and Truesdell, 1921, 1924) and investigations on dogs (Greene and Gilbert, 1922; Sands and DeGraff, 1925) rebreathing through soda lime. Our experimental technic was similar to the technics used for dogs, with the exception that only local anethetics were used in our experiments, whereas in the older investigations chloretone with either ether or morphine was used. As will be shown this makes a great difference in the animals' reactions.

Actually, this type of fatal anoxia does not often happen to man. The only condition which it resembles is that of an aviator flying rapidly to high altitudes without an oxygen supply. The balloon flight of Tissandier, Sivel and Croce-Spinelli in 1875, which only Tissandier survived, induced anoxia of this type (Armstrong, 1939). It has some resemblance to CO-poisoning in that in both types the O_2 content of the blood is progres-

*From the Carter Physiological Laboratory, The University of Texas Medical Branch, Galveston. This paper reports a portion of the results obtained in a program of research on the efficacy of resuscitation procedures. The program is sponsored by the Air Materiel Command, Wright Field, Ohio, under contract No. W 33–038 ac–14379. Received for publication June 22, 1949.

sively reduced; it differs in that in CO-poisoning the arterial O_2-tension is always normal. The two conditions thus furnish an interesting contrast.

Methods

The dog's usual breathing mask (Swann and Brucer, 1949a) was connected with the spirometer of a "Sanborn Waterless Metabolism Tester." The dogs breathed into and out of this system until the oxygen was exhausted, the expired CO_2 being absorbed by soda lime. The starting volume of gas in the system was 3.52 L. of air from the dog's muzzle outwards. The measurements taken are described in the first paper of this series (Swann and Brucer, 1949a), except that the breathing was recorded directly on the kymograph of the metabolism tester.

Results

The results are shown in Tables I, II, III, and IV with a graph of the changes in one dog, No. IV, presented in Figure 1.

The dogs' hearts failed in 15–26 min. With the exception of No. III in which death occurred at a 26 per cent saturation, O_2-saturations at death were about 5 per cent. This shows that the O_2 was thoroughly exhausted from the closed system used. The breathing was strongly stimulated during the progressive anoxia to a ventilation about 10 times greater than the resting ventilation or about 5 times greater than the initial level. The maximum ventilation occurred at O_2-saturations of 25–35 per cent. Respiratory rates are only poorly correlated with ventilation rates, in many cases a high respiratory rate being accompanied with a medium ventilation and vice versa. When the O_2-saturation of the blood fell below 25 per cent, the ventilation fell to a rate about twice that of the resting dog and remained at this level until apnea.

Respiratory arrest occurred suddenly, on the whole, as in the previous experiments, without any long period of "tapering off" or weakening. In all the dogs, the breathing failed, essentially, as the blood pressure was rapidly declining.

TABLE I

Rebreathe Through Soda Lime
Young Adult Male, 8.6 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic / Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.54	1.7	9	16.5	84	44.5	41	23	0	7.34	14.4	7.2	95	194/102	92	10	1
3	.54	1.7	9	16.0	79	47.2	50	23	0	7.29	16.5	6.8	75	196/108	88	13	3
8	1.00	3.1	14	16.3	85	40.4	36	20	0	7.36	14.1	6.8	90	205/100	105	2	—7
12	.88	2.8	5.5	8.1	41	41.6	31	21	0	7.44	14.8	6.8	121	223/130	93	11	—8
17	2.25	7.0	7.5	6.6	34	33.4	18	18	0	7.62			100	285/118	167	—2	—13
20	1.54	4.7	5.5	6.5	35	27.0	14	14	60	7.63	13.5	7.0	48	325/125	200	0	—17
23	.44	1.4	2	2.8	14	27.2	16	14	125	7.58	15.2	7.2	85	278/140	138	0	—23
24	0	0	0	1.6	8	25.1	27	12	150	7.27	15.4	7.4	80	205/50	155	—9	—21
25	0	0	0	0.6	3	24.4	29	12	160	7.23	15.6	7.7	*	—/5	5	—7	—21

*Ventricular fibrillation at 24:45.

TABLE II

Rebreathe Through Soda Lime
Adult Male, 11.8 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.90	2.2	4.5	19.9	100	35.0	34	17	0	7.32	14.2	7.0	169	196	112	84	0	—4
5	1.80	4.4	4.5	15.4	69	34.8	33	17	0	7.34	16.3	7.3	180	240	138	102	15	4
8	4.00	9.8	9	5.5	26	36.9	27	20	0	7.48	15.6	7.0	157	310	155	155	122	60
10	2.64	6.3	6	3.2	14	24.2	17	12	105	7.48		6.9	62	342	132	210	17	0
12	2.08	5.1	4	2.6	11	17.8	13	9	115	7.47	17.0	7.0	61	340	108	232	18	—4
13	1.12	2.7	2										81	312	125	187	19	—5
14	1.00	2.4	5	1.6	7	15.3	14	8	120	7.38	16.8	7.5	113	160	54	106	15	—4
15	0	0	0										160	54	18	36	13	—3
16	0	0	0	1.1	5	18.7	25	10	115	7.20	17.6	7.5	20	3	3	0	12	—4

TABLE III

Rebreathe Through Soda Lime
Adult Female, 10.4 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.90	2.4	5	15.6	82	34.9	39	17	0	7.25	14.0	6.7	69	188	89	99	1	—5
5	1.20	3.2	7	14.8	78	35.6	36	17	0	7.29	13.9	9.3	100	194	86	108	1	—4
8	1.80	4.9	9	11.2	58	34.4	30	17	35	7.37	14.2	6.9	111	210	102	108	1	—4
10	2.85	7.7	9.5	11.9	66	40.6	34	20	36	7.39	13.3	7.7	170	246	115	131	4	—3
14	4.00	10.8	25*	5.0	28	26.0	24	13	65	7.34	13.2	7.1	94	296	87	209	20	4
16	4.80	12.9	24*	4.5	27	23.8	25	12	85	7.28	12.4	6.8	122	310	102	208	28	10
18	2.84	7.7	9.5	4.8	25	17.9	17	9	90	7.33	14.0	7.2	90	351	92	259	14	—2
21	3.38	9.1	12	9.7	50	12.4	14	6	92	7.24	14.3	8.5	87	348	86	262	18	—1
23	2.10	5.7	7	9.9	52	15.1	22	7	99	7.12	14.0	7.5	101	328	92	236	13	—3
24	.40	1.1	1										47	226	40	186	16	—4
25	.40	1.1	5	4.6	26	9.9	16	5	125	7.09	13.0	7.4	23	46	18	28	13	—3
26	0	0	0										0	10	10	0	10	—4
27	0	0	0	5.4	31	11.8	19	5	160	7.07								

*Panting at these times.

TABLE IV

Rebreathe Through Soda Lime
Young Adult Male, 8.7 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.90	2.8	4.8	13.7	83	45.0	43	22	0	7.32	12.2	8.7	120				7	—3
5	.69	2.3	5	11.3	68	45.1	43	22	0	7.32		8.7	115	178	108	70	0	—4
9	1.50	4.7	10	12.4	77	45.5	34	22	10	7.43	11.8	8.4	170	185	97	88	—4	—8
12	1.50	4.7	12	13.5	62	37.9	29	20	20	7.45	16.0	8.6	112	180	127	53	—7	—11
15	3.25	10.0	13	5.9	34	36.7	28	18	60	7.42	12.8	7.9	135	245	100	145	9	—3
19	.84	2.6	3			26.4	19	13	120	7.46	13.7	8.6	52	266	74	192	9	—4
22	1.16	3.6	4	3.4	25	16.4	12	8	200	7.43	10.0	8.8	54	264	82	182	8	—8
25	.72	2.3	3	9.6	61	16.4	17	8	150	7.26	11.6	8.9	63	250	65	185	8	—7
26	.70	2.2	2.5										83	198	44	154	7	—5
27	.30	1.0	3										82	84	23	61	8	—4
28	0	0	0	1.0	5	12.8	23	6	100	7.02	14.8	9.1	3	25	8	17	9	—3
29	0	0	0										12	6	6	0	8	—4

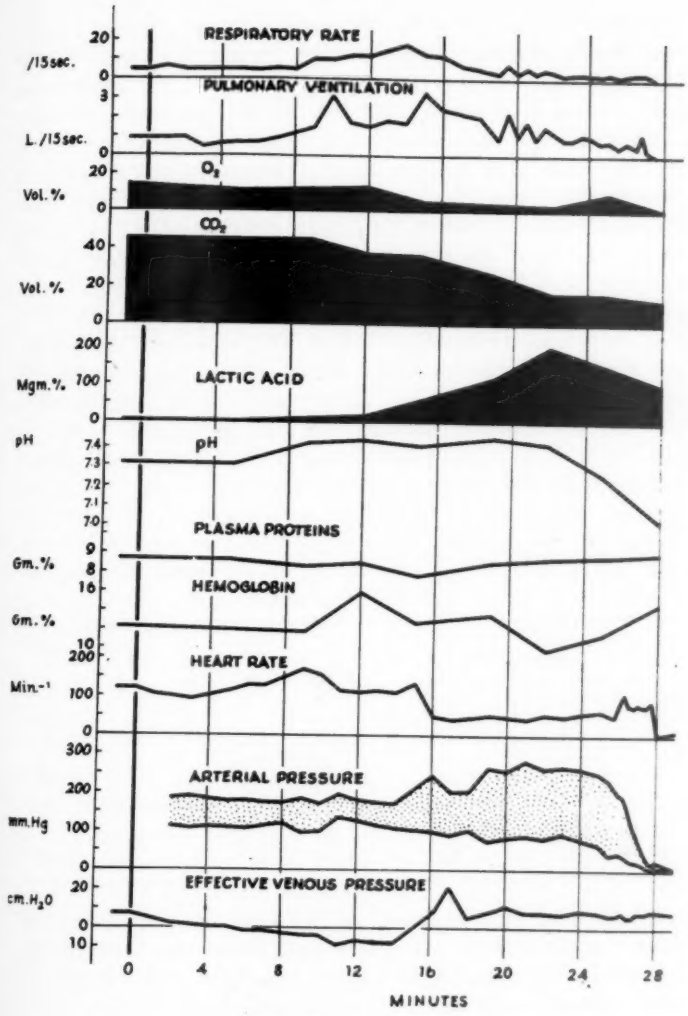

FIGURE 1

Course of progressive anoxia. Dog No. IV.

The overbreathing caused at first a decline in the CO_2-content and tension and with this loss of acid, a rise in pH. During this phase, the alkali reserve remained essentially unchanged. Then as the ventilation rate slowed, the blood lactic acid increased, the pH fell, and the CO_2-content, the CO_2-tension and the blood bicarbonate sharply decreased.

The changes in pulse rate were first a strong increase in rate and then a sudden slowing. The increase appeared with the moderate O_2-desaturations, the slowing with the severe anoxia, *i.e.*, the rate increased as the saturation fell to 25–35 per cent and then it slowed abruptly. The sudden change was striking. Since the tables do not adequately present it, the minute-to-minute heart rates, at the period of change, are shown in Table V; over a period of a minute, in 3 of the 4 dogs, the heart rate was about halved. With the slowing in rate, the diastolic pressure fell and the systolic pressure rose. The hearts continued strong for 6–12 min. thereafter, and then the circulation suddenly failed over a period of about 1 min.

TABLE V

Onset of Bradycardia

No. I	Minute	15	16	17	18	19
	O_2-saturation, %			34		
	Pulse rate, per min.	110	88	100	62	56
No. II	Minute	6	7	8	9	10
	O_2-saturation, %			26		14
	Pulse rate, per min.	190	189	157	77	62
No. III	Minute	10	11	12	13	14
	O_2-saturation, %	66				28
	Pulse rate, per min.	170	189	125	121	94
No. IV	Minute	12	13	14	15	16
	O_2-saturation, %	62			34	
	Pulse rate, per min.	112	115	112	135	48

In the electrocardiograms, the P waves became dissociated from the ventricular complexes just when the bradycardia appeared. They then reappeared irregularly just before systolic collapse, with partial or complete blocks. They then dropped out completely. The ventricular complexes showed gradually lowering voltage of the R waves. Shortly before the period of systolic collapse, the ST segments began to rise and

slur into high peaked T waves. While the ECG was in this phase, systolic collapse occurred. Just after the heart had essentially failed as a pump, dog No. I developed ventricular fibrillation; the other 3 dogs developed deep S waves, with ST segments slurring into a high peaked T wave. The last complexes appeared at 33–40 min., 8–15 min. after heart failure.

The second heart sound disappeared about a minute before the first heart sound, the latter disappearing at the end of the period of collapse when the blood pressure was about 50/20.

Discussion

Three of the dogs survived about 25 min., but one—No. II—only survived 16 min. This dog's arterial O_2-saturation had dropped to 14 per cent by the 10th min., whereas the other dogs' blood O_2-saturation remained high longer. The cause for this rapid desaturation is thought to lie in the respiratory behavior: the dog's breathing was greatly stimulated by the anoxia: to supplement the tabular information, its breathing rose to 2.00 liters per quarter-minute at 6 min., 3.12 L. at 7 min., 4.00 L. at 8 min., and 4.00 L. at 9 min. This overbreathing undoubtedly increased the O_2 demands of the dog, thus probably using up the available supply faster, and hence causing a relatively early death.

The changes in acid-base equilibrium are the ones already familiar to us from the studies of anoxia in dogs while breathing N_2 or 2.43 per cent O_2 (Swann and Brucer, 1949 a and b): first a respiratory—and hematic— alkalosis, followed by a metabolic acidosis from primarily an hyperlactacidemia, with lowered pH and bicarbonate, and a continued fall in pCO_2. Terminally, apnea allows the blood pCO_2 to build up again. As shown in the previous paper, the blood bicarbonate falls as the blood lactic acid rises. When the relation of the two is plotted (see Swann and Brucer, 1949b), it is found that 1 mE./L. of lactic acid preempts 0.86 mE./L. of bicarbonate. Evidently, most of the lactic acid is neutralized by $BHCO_3$.

In the older studies of progressive anoxia on both man and dogs, there appeared a point in the development of the anoxia that was called "the cardio-respiratory crisis" (Greene and Gilbert, 1921) at this point, many changes occurred: first,

a strong vagal slowing of the heart, accompanied with a dropping out of the P waves in the electrocardiogram; second, an abrupt fall in blood pressure; third, depression, and soon failure, of respiration. The heart failed, in the experiments of Greene and Gilbert (1922) in 3–5 min. after the "crisis." In our experiments the heart does not fail and the breathing is not arrested until long after the "crisis." We have found that the "crisis" occurs in a much different form—a difference which we think due to the absence of general anesthesia.

The experiment of Greene and Gilbert (1922) is directly comparable with ours since they employed in 12 of their experiments a rebreather volume of 4.1 L. (3 liters plus 1,100 cc. of "dead space of the apparatus"), while the volume of our apparatus was not far different, viz., 3.5 L. In both experiments, the heart slowed pronouncedly at about 15 min. with AV rhythm becoming dominant. This occurred in their experiment close to respiratory arrest, at an average time of 13 min., 32 sec.; the blood pressure fell to zero some 2 min. later. In our experiment, the cardiac slowing occurred at 16 min., but the breathing did not stop and the circulation did not fail until 7 min. later. Since our dogs' hearts failed on the average 24 min. after the start, our dogs survived some 50 per cent longer than theirs, in spite of the fact that our rebreather space was actually smaller (by 15 per cent) than theirs.

The data on O_2-concentrations further elucidate the situation: Greene and Gilbert (1922) show that the average O_2-content of their rebreather at death (*i.e.*, just after the cardiorespiratory crisis) was 3.26 per cent. Employing the formula of Horvath, Dill, and Corwin (1943),

$$pO_2 = F_{O_2} (760 - pH_2O - pCO_2)$$

in which the symbol p represents the alveolar tension of these gases and F_{O_2} represents the fraction of O_2 breathed, and assuming pCO_2 is 25, the alveolar pO_2 in their dogs was 22 mm. Hg. This corresponds, at a pH of 7.2, to an oxygen saturation of about 30 per cent. In our experiment, the bradycardia occurred at 25–35 per cent saturation, so evidently both groups

of dogs experienced the bradycardia at about the same O_2-saturations and the same time. The difference is that whereas their dogs stopped breathing, ours continued, and our dogs' lives for this reason were greatly prolonged. The difference in behavior is undoubtedly due to anesthesia: in the anesthetized dog, the breathing fails much sooner than in the unanesthetized dog (Swann, Wilson, and Barry, 1945). In the dogs of Greene and Gilbert (1922)—they used chloretone or chloretone and ether anesthesia—breathing stopped when the "cardiac crisis" occurred, and death, due to the anoxia of apnea soon took place, whereas in our dogs, though the breathing slowed at the "crisis," it did not stop and the animals continued living for a long period.

A comparison like this cannot be made with the experiment of Sands and DeGraff (1925) because their dogs were breathing into a rebreather of 25 L. capacity and lived about 90 min. These workers reported that the "crisis" occurred when the O_2 of the inspired air had decreased to 9 or 10 per cent—a result almost incomprehensible to us, because at this degree of anoxia, the blood of living dogs, unless they are very deeply anesthetized, is still 70 to 90 per cent saturated with O_2 and the animals are in good condition (see also Chambers, etc., 1947). In the 2 protocols shown in the report of Sands and DeGraff (1925), death occurred some 20 min. after the crisis, at times when the oxygen content in the rebreather was 5 per cent. These dogs, therefore, anesthetized as they were with chloretone and morphine, appear to have died at even higher O_2-saturations than the dogs of Greene and Gilbert (1922).

In summary, in all of the experiments so far reported, we have found that after the O_2-saturation falls to 10–13 per cent or lower, the dog survives only 2–5 min. Until this saturation is reached, in the absence of general anesthesia, the breathing and heart continue strong. Stacy, Whitehorn, and Hitchcock (1948) have come to similar conclusions.

The effects on heart rate and blood pressure which we have found confirm the previous reports of Greene and Gilbert (1922) and Sands and DeGraff (1925). The rate increases and both systolic and diastolic pressures increase until the "crisis" is reached. Sands and DeGraff (1925) found that the

effective venous pressure increases sharply just at the beginning of the "crisis"; and Wiggers (1941) ascribes the "crisis" to acute congestive heart failure. Our data fail to show this phenomenon, either at the time of first cardiac slowing or at the time of circulatory failure. As discussed previously (Swann and Brucer, 1949a), the only point at which we felt confident that a demonstrable rise in effective venous pressure had occurred was in the nembutalized dog breathing N_2. It seems probable that here is still another change that occurs predictably only when the general anesthesia is used.

The set of events called "the cardio-respiratory crisis" was usually considered by other investigators to be the immediate precursor and harbinger of death. In our opinion, this point of view is wrong: in the first place, the use of general anesthetics has given results (see also Robbins, Fitzhugh, and Baxter, 1939 and Allen, Echols, Hoeflich, O'Neal, and Slocum, 1947), sharply different from those observed in the absence of general anesthesia. In the second place, the three cardinal events of the "cardio-respiratory crisis"—*bradycardia* shortly followed by *failing respiration* and then *circulatory failure*—appear consistently, in the absence of general anesthesia, in only fulminating anoxia, *i.e.*, while breathing pure N_2. They do not appear in acute or progressive anoxia, nor, as will be shown, in CO-poisoning or obstructive asphyxia or drowning.

We have used the phrase "general anesthesia" somewhat negligently, particularly in view of the recent demonstration by Allen, Echols, Hoeflich, O'Neal, and Slocum (1947) that the various general anesthetics cause sharply different reactions to fulminating anoxia in the dog. It is impossible to say whether or not our conclusions hold for *all* general anesthetics. However, we feel certain that they hold for barbiturate anesthesia and for any experiments in which morphine is used, since both of these drugs are such strong respiratory depressants. At all events, we shall employ the phrase "general anesthesia" to indicate loosely our belief that general anesthesia of whatever type will give results in studying anoxia which are far different from the results obtained in its absence. Certainly, this is justified while discussing canine physiology

where the barbiturates and morphine are so frequently employed.

From the discussion of this paper, it is apparent that in progressive anoxia, a "cardio-respiratory crisis" does not take place in the unanesthetized dog: there occurs long before death a strong bradycardia; soon thereafter the lung ventilation is lessened, but the breathing and heart continue for some time, until finally both fail. The failure should best be considered as simultaneous, with neither the one nor the other preceding. If general anesthesia is used, it is suggested that the breathing fails at about the time of the bradycardia, this being at O_2-saturations of about 30 per cent. Then the heart quickly fails from the anoxia of apnea. General anesthesia, in effect, terminates life soon after 30 per cent O_2-saturation is reached; without general anesthesia, life continues to O_2-saturations far below 30 per cent.

We are now in a position to summarize the terminal cardio-respiratory changes in the three types of anoxia so far studied. Taking first the cardiac behavior, at O_2-saturations of 80–30 per cent the heart accelerates greatly, but if the saturation falls below 30 per cent, a sudden strong slowing occurs, vagally induced, with abolition of the P wave in the electrocardiogram. If the dog's O_2-saturation is suddenly dropped below 30 per cent, as in breathing N_2, slowing but not acceleration occurs. Terminally, as the circulation is failing, irregular tachycardia may be observed. Thus the dictum that anoxia causes cardio-acceleration is true only for certain ranges of anoxia. When the heart slows, it is by no means a sign of impending death, for we have observed dogs to live for 20 or even 30 min. beyond the onset of the bradycardia (Swann and Brucer, 1949b). With the slowing of the heart, the diastolic pressure falls sharply and the systolic pressure rises sharply. With a mercury manometer, this is often read as a low blood pressure, but actually, with the high pulse pressures, the heart is by no means failing, but rather is circulating the blood very effectively and is doing very much work.

The pulmonary ventilation follows a similar pattern: strong stimulation in moderate anoxia, less volume in strong anoxia,

and finally apnea in extreme anoxia. In another paper (Brucer, Levy, and Swann, 1949), we will show that the breathing (VR) is best related to the O_2-saturation (Os) by this cubic equation:

$$VR = 2.540 - 2.85\ Os - 0.237\ Os^2 - 0.005\ Os^3.$$

The pulmonary ventilation just before death does not (for the dog at any rate) slow or taper off or become so small in volume as to be virtually imperceptible, as is reported to happen in man (Haldane and Priestley, 1935; Drinker, 1944). We find no evidence for "fatigue of the respiratory center," with rapid shallow breathing, as described by Haldane and Priestley (1935). Rather, as reported by Chambers, Brewer, Davenport, and Goldschmidt (1947) and as found in these studies, the breathing continues at a volume well above the resting level until suddenly apnea supervenes. Sometimes a short period of gasping occurs and sometimes not (Swann, Wilson, and Barry, 1945).

The heart fails, with respect to the breathing, at different times, depending on the type of anoxia. In N_2 anoxia, it fails some 2–3 min. after apnea; in acute or progressive anoxia, it fails sometimes before, sometimes simultaneously, and sometimes after apnea. It is the general belief that the breathing fails before the heart in anoxia: Haldane and Priestley (1935) say "Respiration seems almost always to fail before the heart fails"; Peters and Van Slyke (1932) suggest that it fails 6–8 min. beforehand; Drinker (1944, 1945) states that it is a "matter of minutes" and implies that it may be in some cases 12 min. While this conclusion may hold for man, it does not hold for dogs. We suspect also that the conclusion derives mostly from studies on anesthetized animals and that therefore death has been hastened by causing apnea at relatively high O_2-saturations. As we have pointed out in this paper, in general anesthesia the breathing probably stops at O_2-saturations of about 30 per cent, while without general anesthesia it continues actively to much lower O_2-saturations.

SUMMARY

Simultaneous measurements are reported of the breathing, systolic and diastolic blood pressures, effective venous pressure, electrocardiograms, heart sounds, blood gases, pH, lactic acid, hemoglobin, and plasma proteins of dogs, under local anesthesia, during progressive anoxic death caused by rebreathing air through soda lime.

In contrasting the results obtained with reports by previous studies, the conclusion is drawn that the so-called "cardiorespiratory crisis" only occurs in the anoxia of breathing pure nitrogen. It has been observed in other types of anoxia mainly because general anesthetics hasten death by causing apnea at relatively high oxygen saturations. The changes in breathing and heart rate in three types of anoxia are summarized: in moderate anoxia, high lung ventilation and heart rate, in strong anoxia, low but adequate ventilation and bradycardia, and in extreme anoxia, apnea and strong bradycardia. In fulminating anoxia, breathing stops some 2 or 3 min. before circulatory failure, but in acute and progressive anoxia breathing fails now before, now after, and now simultaneously with circulatory failure. When the arterial blood oxygen saturation falls to 12 per cent or less, dogs survive only 2–5 min.

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THE CARDIORESPIRATORY AND BIOCHEMICAL EVENTS DURING RAPID ANOXIC DEATH

IV. CARBON MONOXIDE POISONING*

H. G. Swann and Marshall Brucer

Of all types of overwhelming accidents, carbon monoxide poisoning has been most thoroughly studied following the classic study of Bernard (1857). Recent comprehensive reviews of this topic have been made by Sayers and Davenport (1936), Drinker (1938), Killick (1940) and Von Oettingen (1944). The careful study by Yant, Chronyak, Schrenk, Patty and Sayers (1934) on blood chemical changes was done without the superimposed complication of general anesthesia but it includes no data on the cardiorespiratory changes; the equally thorough study of Von Oettingen, Donahue, Valaer and Miller (1941) was done under the general anesthetic amytal. It was therefore thought advisable to restudy CO-poisoning, avoiding general anesthesia and utilizing the same measurements and conditions employed in our entire investigation of the process of death. Therefore a study of the behavior of dogs breathing 1 per cent CO in air was made; this is a relatively toxic concentration of CO to the dog, causing death in from 16 to 25 min.

Methods

Carbon monoxide was prepared by the interaction of sulfuric acid and formic acid, passed over KOH (Peters and Van Slyke, 1932), and then diluted with 99 volumes of air in a spirometer. This was given to the dogs to breathe by the method previously described (Swann and Brucer, 1949a). The CO-content of the dog's arterial blood was measured by the method of Van Slyke and Neill (1924). The measurements of breathing, arterial and venous and intrathoracic pressures, and blood gases, pH,

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etc. were made by methods already described (Swann and Brucer, 1949a).

In computing the O_2- and CO-saturations, the capacities were estimated from the assumption that each gram of hemoglobin carries 1.36 cc. of O_2 or CO. As was previously discussed (Swann and Brucer, 1949a), this leads to false results in some instances, *e.g.*, at the second minute in dog IV, it gives the statement that the arterial blood was 100 per cent saturated with O_2 and 12 per cent saturated with CO. Our estimates, then, are admittedly inaccurate, but even so they are critical in evaluating the dogs' physiological status.

Results

The results in four dogs are shown in Tables I, II, III and IV, with a graph of the changes in one dog, No. III, in Figure 1.

The breathing of the dogs followed a characteristic pattern: as the O_2-saturation was decreasing, the pulmonary ventilation increased to about double the initial rate. This occurred at O_2-saturations of 20–40 per cent. Then when the O_2-saturation fell further to 10–12 per cent, the lung ventilation decreased. After this point it became very irregular: now high, now even stopping briefly (see Figure 1). Just before respiratory arrest, there was more "tapering off" of respiration than appeared in the dogs breathing 2.43 per cent O_2 (Swann and Brucer, 1949b). However, even here, the breathing could not be called "faint" or "barely perceptible" for the tidal volumes were 40–100 cc., the rates were about 3 per 15 sec., and the lung ventilation was about the same as at rest (see tables). A distinct decrease in the respiration occurred at about the time arterial O_2-saturation first dropped to 12–14 per cent. This recalls the point of cessation of eupnea in dogs breathing N_2 (Swann and Brucer, 1949a). In the dogs breathing 1 per cent CO, however after this temporary decrease, the respiration became high again. Respiratory arrest occurred at approximately the same time that circulation failed. In one dog—No. III—breathing continued for a short time after the heart had failed. Death occurred at CO-saturations of 80–90 per

cent. However, the dogs had reached this level of saturation long before the heart failed, *i.e.*, 10, 10, 9 and 8 min. respectively.

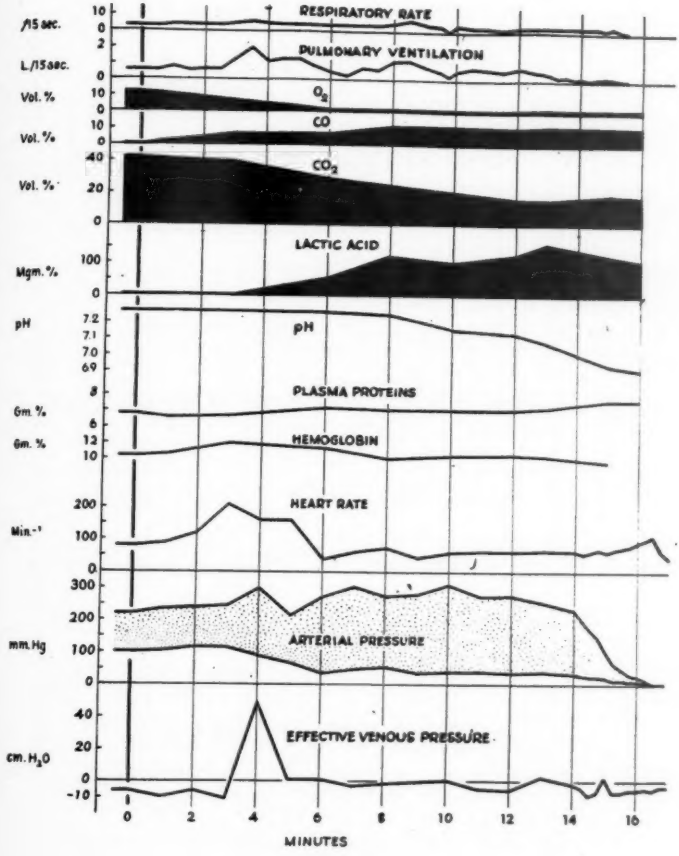

FIGURE 1

Course of carbon monoxide poisoning. Dog No. III.

TABLE I

1% Carbon Monoxide in Air
Adult Male, 7.1 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO, vols. %	Arterial CO saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic / Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.56	2.0	3	11.8	83	0	0	41.5	43	19	0	7.27	10.4	6.8	79	218/100	118	—6	—9
1	.80	2.9	4	10.2	71	2.2	15	40.5	42	19	0	7.27	10.6	6.6	89	235/105	130	—10	—13
3	1.34	4.9	5	6.7	41	6.6	40	39.5	39	17	0	7.27	12.0	6.7	210	244/116	128	—11	—18
6	.50	1.8	4	1.5	10			28.9	30	13	56	7.27	11.4	7.2	38	271/36	235	1	—13
8	1.13	4.1	5	1.4	10	11.5	84	24.3	26	11	125	7.25	10.1	7.1	74	274/54	220	—2	—11
10	.55	2.0	4	1.3	9	11.5	81	20.5	27	10	105	7.16	10.5	7.1	59	308/40	268	0	—13
12	.75	2.7	3	1.4	10	10.8	75	16.2	22	7	128	7.13	10.6	7.1	62	276/36	240	—6	—14
13	.36	1.3	3	2.0	14	11.9	84	16.0	24	7	140	7.08	10.4	7.2	65	256/38	218	2	—6
14	.14	.5	3												64	230/32	198	—2	—14
15	.12	.4	3	1.4	11	11.2	85	18.9	38	8	125	6.94	10.1	7.7	60	98/18	80	2	—16
16	0		0	1.8	13	10.7	79	17.6	38	8	108	6.91		7.7	88	22/9	13	—6	—12

TABLE II

1% Carbon Monoxide in Air
Adult Male, 7.5 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO, vols. %	Arterial CO saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic / Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.84	2.9	3	16.6	100	0	0	37.7	41	18	0	7.25	12.2	6.1	142	258/118	140	33	12
2	.72	2.5	3	12.8	71	4.0	22	37.3	42	18	0	7.24	13.3	6.3	142	232/116	116	31	12
5	1.04	3.6	3.5	4.7	27	13.3	76	33.8	42	16	25	7.19	13.0	6.4	160	265/95	170	26	10
8	.85	3.0	2.5	2.0	12	15.6	90	24.7	25	12	100	7.27			27	312/38	274	32	5
12	1.10	3.9	6	1.8	11	16.6	98	15.8	24	7	200	7.10	12.5	6.8	132	310/82	228	22	3
13	.21	.7	3	1.6	9	15.9	92	12.2	18	6	200	7.10		6.8	15	232/27	205	31	0
14	.33	1.2	8												80	205/30	175	21	4
15	0		0	1.8	10	13.9	80	20.3	48	9	200	6.87	12.8	7.7	125	70/18	52	20	4
16	0		0												50	18/5	13	20	4
17	0		0												18	5/5	0	20	4

TABLE III
1% Carbon Monoxide in Air
Adult Female, 8.3 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO, vols. %	Arterial CO saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	1.00	3.2	7.5	19.6	85	0	0	36.5	34	19	0	7.36	17.0	7.3	88	232	122	110	11	0
1	1.05	3.4	10.0	16.5	70	1.8	4	36.2	36	18		7.33	17.4	7.0	81	225	107	118	11	—4
3	1.15	3.7	8.5	13.9	71	5.7	29	36.2	37	18	0	7.30	14.4	7.3	117	241	130	111	16	—3
5	2.37	7.7	8	7.8	39	7.6	38	34.6	36	17	0	7.29	14.8	7.1	289	290	120	170		
7	1.30	4.2	6.5	3.5	18	16.0	81	30.0	33	14	55	7.26	14.6	7.1	150	312	134	178		
10	.30	1.0	3	2.2	12	17.4	98	24.5	30	12	56	7.20	13.0	7.1	78	312	98	214	—9	—19
13	1.25	4.0	7	2.0	12	17.2	100	17.7	23	8	70	7.16		7.1	85	323	80	243	—27	—36
16	.73	2.4	3	1.7	10	17.7	100	15.3	24	7	125	7.08	12.0	6.8	92	262	62	200	13	1
17	.46	1.5	2												94	250	62	188	7	—2
18	.15	.5	4	2.5	11	17.4	75	19.4	45	9	125	6.91	17.1	7.8	79	100	18	82	5	—1
19	0	0	0	2.5	15	17.6	100	20.5	52	9	100	6.86	12.5	7.0	55	29	8	21	3	—3
20	.05	.2	1												28	9	5	4	4	—3
21	0		0												7	5	5	0	3	—3

TABLE IV

1% Carbon Monoxide in Air
Adult Female, 5.9 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO, vols. %	Arterial CO saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.50	2.1	3.5	24.9	100	0	0	32.1	34	16	0	7.29	15.4	7.0	88	223	116	107	11	1
2	.41	1.7	4	21.6	100	2.5	12	31.2	33	15	0	7.29	15.4	6.5	95	223	116	107	6	—2
6	.61	2.6	5	17.2	83	5.5	26	30.4	33	15	0	7.27	15.4	7.0	136	220	118	102	7	0
10	1.00	4.2	8	6.5	30	13.9	64	30.7	34	15	0	7.26	16.0	6.4	108	243	100	143	13	4
13	.65	2.7	5	2.8	13	14.4	66	30.0	33	14	25	7.26	16.1	6.1	100	260	80	180	1	—6
15	.40	1.7	5	3.0	14	15.9	76	23.7	28	11		7.23	15.5	6.6	42	300	38	262	7	—6
17	.80	3.4	3.5	3.2	15	16.1	75	20.8	26	10	75	7.20	15.8	7.0	91	278	65	213	8	—2
20	.15	.6	1	2.3	10	16.5	75	12.7	19	6		7.11	17.0	6.7	21	276	18	258	11	—3
22	.52	2.2	2.5												71	250	45	205	4	—3
23	.24	1.0	3.5	2.0	13	13.8	86	12.4	26	5		6.93	11.8	7.3	43	178	14	164	3	—3
24	.05	.2	3												62	87	15	72	0	—3
25	0		0												135	16	5	11	3	—3
26	0		0												*	—	5	0	5	—3

*Ventricular fibrillation at 25:10.

In confirmation of Yant, Chornyak, Schrenk, Patty and Sayers (1934), the CO_2-content and the CO_2-tension decreased all through the experiment, except that just as breathing was failing, the CO_2-tension rose sharply. The pH fell slowly until just at death, when it fell precipitously.

Heart rates first increased; they then abruptly decreased at the time that arterial O_2-saturation had fallen to 10–15 per cent. Rates of 20 to 30 min. were not uncommon, with very low diastolic pressures accompanying the bradycardia. As heart failure became imminent, a sharp decrease in systolic pressure was apparent. A flurry of rapid heart beats appeared when the heart was failing, dog No. III excepted.

In the electrocardiograms the P waves disappeared at 6, 8, 10 and 12 min. in the 4 dogs, just at the time when the arterial O_2-saturation fell to 10–15 per cent. In all but one dog the P waves reappeared at the beginning of the period of systolic collapse and then disappeared. The QRST complex decreased to a very low voltage; at the time of systolic collapse it consisted of simple monophasic QRS waves, a long isoelectric ST segment and a single monophasic T in opposite phase from the QRS.

Ventricular fibrillation appeared in the records of dog No. IV at 25 min. 10 sec., just as the period of systolic collapse was ending. In 2 other dogs ventricular fibrillation appeared about to begin, but the ventricular complexes quickly reverted to rhythmic impulses. The last complexes appeared at 20–27 min., some 3–10 min. after the heart had failed as a pump.

The second heart sound disappeared when the systolic blood pressure was decreasing. The first sound disappeared about a minute later when the diastolic pressure reached 8–15 mm. Hg.

Discussion

The chemical changes which we have found match closely those reported by Yant, Chornyak, Schrenk, Patty and Sayers (1934) in unanesthetized dogs breathing 0.6 per cent CO: in both experiments, the dogs died at CO-saturations of about 90 per cent; in both the O_2-content was very low at death; in both the CO_2-content decreased markedly; in both the pH

declined; and in both the hemoglobin content remained unchanged. Their dogs survived from 21–31 min., ours 16–24 min., a difference no doubt due to the fact that they were using a lower concentration of CO than we were. We found the CO_2-content and the pH of the blood to be more strongly decreased at death than they did, a difference perhaps due to a stronger lactacidemia (see below) in our condition of more rapid CO-poisoning.

Von Oettingen, Donahue, Valaer and Miller (1941) also measured the cardiorespiratory, chemical and other changes in dogs breathing 1 per cent CO just as we have done. Their animals, however, were anesthetized with sodium amytal, and this fact serves to point up sharply the differences in behavior of anesthetized and unanesthetized dogs: their dogs died on an average at 28 min., ours at 19 min. This difference is thought due to the rates of intoxication in the two experiments. Since their dogs' respiration was considerably depressed by the amytal, averaging at the control reading 1.1 L./min. while our dogs' respiration averaged 2.9 L./min., and since it is well recognized that exercise and a rapid respiration facilitate CO absorption (Henderson, Haggard, Teague, Prince and Wunderlich, 1921; Sayers, Meriwether and Yant, 1922), our dogs presumably became saturated with CO more rapidly and so died sooner. Both groups of dogs it is to be noted, experienced about a doubling of the lung ventilation, but the levels of ventilation in our dogs were about three times greater than those of Von Oettingen, Donahue, Valaer and Miller (1941). The depressed respiration in their dogs is thought to be responsible for the considerable "piling-up" of CO_2 during their experiment; in unanesthetized dogs, as found by both Yant, Chornyak, Schrenk, Patty and Sayers (1934) and ourselves, the blood CO_2-content decreased.

Respiratory arrest occurred in the dogs of Von Oettingen, Donahue, Valaer and Miller (1941) some 4 min. before circulatory failure whereas in our experience respiratory arrest occurred simultaneously with circulatory failure. This also is thought due to the respiratory depression of anesthetized dogs: they do not respond to the stimulus of anoxia (Swann, Wilson and Barry, 1945; Swann and Brucer, 1949c) and therefore

the breathing stops relatively early. If the breathing had continued, the heart would have continued to receive blood having roughly 2 vols. per cent O_2 in it, or enough to keep the heart pumping for a long time (see below). The relatively "early" death due to apnea in their anesthetized dogs is accompanied with a lower CO-saturation at death than we observed: the dogs of Von Oettingen, Donahue, Valaer and Miller (1941) died at 82 per cent CO-saturation, whereas ours died at about 90 per cent saturation.

A comparison of the blood pressure changes is difficult, because Von Oettingen, Donahue, Valaer and Miller (1941) were employing a mercury manometer whereas we were employing an optical system that recorded both systolic and diastolic pressures. If we assume that our measurements of diastolic pressure are approximately the same as the blood pressures reported by Von Oettingen, Donahue, Valaer and Miller (1941), there is good agreement between the two experiments: we observed (in some of the dogs) the same early pressure rise and the same early tachycardia. There then appeared the same long slow decline of the (diastolic) pressure until death, with the same slowing of the heart. The decline in diastolic pressure, however, is not to be interpreted as a sign of failing cardiac function, because it is accompanied with a pronounced rise in systolic pressures and resulting pulse pressures of 200–250 mm. Hg. The high pulse pressures at once suggest that cardiac outputs and cardiac efficiency remained high for a long time, a fact already demonstrated for moderate CO-poisoning by Chiodi, Dill, Consolazio and Horvath (1941).

The law of Douglas, Haldane and Haldane (1912) states: "When . . . hemoglobin . . . is saturated in the presence of a gas mixture containing O_2 and CO, the ratio of oxyhemoglobin to CO-hemoglobinis always proportional to the relative partial pressures of O_2 and CO . . .," allowing for the fact that the affinity of CO for hemoglobin is much greater than that of O_2, or

$$\frac{(HbCO)}{(HbO_2)} = K\frac{pCO}{pO_2}$$

in which pCO and pO_2 represent the tensions of CO and O_2, and K is the affinity constant (210 for human blood, Sendroy, Liu and Van Slyke, 1929). Applying this law to our experimental conditions, in which CO was at 1 per cent,

$$\frac{(HbCO)}{(HbO_2)} = 210\,\frac{7.6}{160} = \frac{10}{1}$$

or these dogs' arterial hemoglobins should have been about 90 per cent saturated with CO, and 10 per cent saturated with oxygen. This by and large is true (see tables); the dogs all died with a CO-saturation of about 90 per cent. In the experiments of Yant, Chornyak, Schrenk, Patty and Sayers (1934), the dogs also died at about 90 per cent CO-saturation. The deviations from the law are undoubtedly due to differing affinity constants in the separate dogs (see Douglas and Haldane, 1911; Sendroy, Liu and Van Slyke, 1929). It is notable however that the dogs all lived some 9 min. after reaching 90 per cent CO-saturation. They reached this saturation at differing times, *i.e.*, 6, 8, 10 and 13 min. after the start, respectively, and they lived 10, 8, 9 and 11 min. respectively beyond this point. This fact explains the variability in survival of these dogs; those that became saturated with CO earlier died sooner.

Now the factors influencing rate of saturation with CO are very numerous (Sayers and Davenport, 1936; Von Oettingen, 1944). In particular, more rapid pulmonary ventilation leads to more rapid saturation (Henderson, Haggard, Teague, Prince and Wunderlich, 1921; Sayers, Meriwether and Yant, 1922). Although, as discussed above, we suspect this factor is at work in influencing the relative survival time of anesthetized and unanesthetized dogs, it does not appear to be at work in the 4 dogs of our experiment, since the early ventilation rates of the two long-surviving dogs (Nos. III and IV) were as high as or higher than the rates of the two short-surviving dogs. However, the hemoglobin levels of the dogs do appear to influence the rate of CO-saturation and therefore the length of survival; the two long-survivors (Nos. III and IV) had 17 and 15 gm. per cent hemoglobin, whereas the two short-survivors had 10 and 12 gm. per cent. Presumably, the higher the dog's hemoglobin,

the longer the dog survived. This hypothesis is tentative; it is in accord with previous studies which show that anemia greatly decreases resistance to CO-poisoning (Smith, McMillan and Mack, 1935; Von Oettingen, 1944).

It is still a puzzle to us why these four dogs lived for some 9 min. after their blood O_2-saturation had reached 10–12 per cent, because the dogs breathing N_2 or 2.43 per cent O_2 or rebreathing through soda lime (Swann and Brucer, 1949 a,b,c) all died 2–5 min. after their O_2-saturation had fallen to 12 per cent. The uniformity of the appearance of this phenomenon in CO-poisoning is striking: although the four dogs reached the point of 90 per cent saturation of their hemoglobin with CO and 10 per cent saturation with O_2 at different times, each dog lived about 9 min. longer. The phenomenon is still more puzzling when one considers the effect of CO on the O_2-dissociation curve of the hemoglobin in the body not already bound to CO: as shown by Douglas, Haldane and Haldane (1912) and Stadie and Martin (1925), the residual HbO_2 only dissociates under abnormally low O_2 tensions; it "clings to its oxygen with abnormal tenacity" (Peters and Van Slyke, 1932). This means that an O_2-saturation of 10 per cent is a much more severe anoxia in CO-poisoning than in, say, the anoxia of breathing 2.43 per cent O_2. It should have made our CO-poisoned dogs die sooner, whereas in fact they died later than dogs with an equivalent anoxia from other causes. Because the phenomenon appeared so uniformly, we are inclined to believe that our analytical methods have not given us any essentially false information. Although it is known that CO does increase the oxygenation of the blood under low O_2-tensions (Haldane and Smith, 1897; Roughton and Darling, 1944), this effect would not have occurred in our experiments because the pO_2 was normal.

One explanation might be that a splenic contraction some 10 min. before death forced fresh red cells, unpoisoned with CO, into the circulation, thus improving temporarily the O_2-carriage of blood (Barcroft, Murray, Orahovats, Sands and Weiss, 1925; Barcroft, 1938). In our dogs, however, the blood hemoglobins did not rise uniformly, and so probably no considerable splenic contraction took place. Although DeBoer and

Carroll (1924) reported such an occurrence in cats during CO-poisoning, their experiments were done on cats anesthetized with luminal, in which the spleen is widely dilated to start with (Hausner and Mann, 1938; Wiggers, 1942) and so is capable of such a reaction. In unanesthetized dogs the reaction does not occur (Swann and Brucer, 1949a).

Another possible explanation might lie in the rate of utilization of O_2 by the breathing musculature. If the CO dogs are only breathing lightly (as will be shown below), they would presumably burn the available O_2 slower. However, we can readily point to another group of dogs which was virtually apneic and yet died quickly, *i.e.*, those breathing N_2 (Swann and Brucer, 1949a) and so this explanation also appears invalid.

Still another possible explanation is to be found in the behavior of the blood lactic acid and CO_2-tension: the former starts to rise and the latter to fall in all cases at about 10 min. before death. Now although neither of these chemicals influence the final equilibrium of O_2 and CO with hemoglobin (Douglas, Haldane and Haldane, 1912), in both cases they would, if suddenly changed as in our dogs, decrease transiently the CO-saturation (see also Stadie and Martin, 1925). However, this postulated transient decrease in CO-saturation is not apparent in our data. Hence, this explanation also appears untenable.

At present, we are inclined to ascribe the relatively long survival of the CO dogs to the fact that the O_2-tension of their arterial blood is normal. As Asmussen and Chiodi (1941) point out, with the arterial pO_2 normal in CO-poisoning, there is no stimulus to breathing. One might expect therefore that the breathing would continue *ad infinitum*. However, the heart cannot live indefinitely on the pO_2 of plasma exposed to air (although it can live on the pO_2 of plasma exposed to O_2, as in perfusion experiments). Therefore, the heart would start to fail *before* the respiration; when it fails, the breathing would also cease because of anoxia of mechanisms controlling breathing. This hypothesis is confirmed by our data, for in each dog the breathing stopped only after the heart had started to fail, that is, after the pulse pressure had fallen below 100 mm. Hg.

But in the dogs breathing N_2 or 2.43 per cent O_2, the pO_2 was depressed early, and so respiratory and cardiac failure took place sooner. This theory implies that plasma O_2 is more available than hemoglobin O_2 at low saturations—an implication that is difficult to support. Nevertheless, the hypothesis helps explain the observed facts.

We have dwelt on this phenomenon at considerable length because it is thought to be of cardinal importance in the problem of resuscitation from CO-poisoning. As has been shown (Swann, 1949), the heart and breathing of CO-poisoned dogs can be readily restored by insufflating their lungs with O_2 when the heart is failing, *i.e.*, when the systolic blood pressure has fallen to, but not below, 100 mm. Hg. But, with rare exceptions, these "resuscitated" dogs have by that time undergone irreversible anoxic cerebral damage and die in a few days. (By definition this cannot be called successful resuscitation.) In contrast, when dogs are resuscitated from fulminating or acute anoxia when the heart is failing, recovery is normal. The difference is thought to lie in the facts discussed above, *i.e.*, the CO-poisoned dogs live some 9 min. beyond the point at which the O_2-saturation falls to 12 per cent. They apparently continue to breathe and circulation continues to be effective at a time when irreversible cerebral damage has already commenced, whereas in fulminating and acute anoxia, both respiration and the circulation fail before irreversible cerebral damage begins. In fulminating anoxia, irreversible cerebral damage does not start until 3 min. after the heart fails and in acute anoxia it does not start until 1 min. after the heart fails (Swann, 1949).

The breathing, as shown in the tables, increased slightly as the blood was becoming unsaturated with O_2, but then became very irregular and unpredictable. This confirms previous reports that by and large CO-poisoning does not cause much increased breathing in unanesthetized dogs (Asmussen and Chiodi, 1941; Chiodi, Dill, Consolazio and Horvath, 1941). The mild increases we noted at oxygen saturation of 20–40 per cent did not appear in the experiments of Asmussen and Chiodi (1941) because they were dealing with O_2-saturations of 50 per cent or greater. It is clearly shown by our experiment that in

the unanesthetized dog, the anoxia consequent to CO-poisoning does not exert as strong a stimulus to breathing as other types of anoxia, *e.g.*, in the progressive anoxia of rebreathing through soda lime, ten-fold increases in pulmonary ventilation are common (Swann and Brucer, 1949c). Comroe and Schmidt (1938) explain this phenomenon by pointing out that presumably the arterial O_2-tension is the adequate stimulas to the carotid sinus for increasing breathing and that since the pO_2 is not affected by CO, the breathing is not stimulated by the anoxia of CO-poisoning.

The conclusion that CO affects the pulmonary ventilation only mildly is at variance with the report of Haggard and Henderson (1921) that in unanesthetized dogs breathing 0.15 to 0.45 per cent CO there is hyperventilation and acapnia. Their data show 2–3 fold increases in ventilation. We do not consider this a great hyperventilation—it is, of course, small when one considers the ten-fold increases that are readily observed in strong anoxia. In the unanesthetized dog, three-fold increases in ventilation are often seen during the mild struggling and restlessness that are concommitants of restraint. Hence we suspect that the over-breathing reported by Haggard and Henderson (1921) should best be labelled as "slight" and that the dog resembles the human (Haldane, 1895) in that in the absence of anesthesia, CO-poisoning results in only a slight respiratory stimulus.

Many events center around the time at which the dogs' bloods become 90 per cent saturated with CO with a consequent 10 per cent saturation with O_2: the animals have a convulsive seizure of the clonic type, their breathing slows, even to temporary arrest, the blood lactic acid commences to rise, the heart slows abruptly, the rate often being halved over a period of 30 sec., the P waves drop out of the electrocardiogram, and with the bradycardia, the diastolic pressure falls abruptly and the systolic pressure increases sharply.

In recent study of resuscitation in CO-poisoning, Schwerma, Ivy, Friedman and La Brosse (1948), employing 0.3 per cent CO (with other gases, since the source of CO was a gas main), have used as criterion of the imminence of death the first appearance of "air hunger . . . characterized by a spasmodic

contraction of the depressor muscles of the mandible which in many dogs was accompanied by a generalized extensor spasm." The dogs lived from 1 to 9 min. after this sign. It seems probable to us that they were dealing in many dogs with the point at which the O_2-saturation first reached its lowest level. However, the fact that they reported the dogs live from 1 to 9 min. beyond this point does not agree with our finding that the dogs live uniformly some 9 min. beyond this point. The fact that they were using 0.3 per cent CO whereas we were using 1 per cent CO may account for this. But also it seems to us probable that because dogs frequently have several of these attacks of "air hunger" before death (in our experience at any time for ½ min. to 11 min. before death), their selection of the first attack of air hunger was not uniform. In our experience a selection like this would, at best, be difficult. It is obviously not an objective measurement.

The changes found in acid-base equilibrium agree with the universal finding that a metabolic acidosis occurs in CO-poisoning (Von Oettingen, 1944). Although early in the experiment these dogs became mildly hyperpneic, they evidently, as the data show, did not overbreathe enough to change the CO_2-content or tension. After the breathing had returned to the initial level, the blood lactic commenced to increase, and simultaneously in most instances, the blood pH started to fall. At the same time, the CO_2-content, pCO_2 and blood bicarbonate all started to decrease. Because the increase in acidity was not accompanied with any increases in CO_2 in any form, the acidocis cannot be due to CO_2-excess. Rather, many acids increase at this point; lactic acid, as shown in our data, confirming many observers (Araki, 1891; see Von Oettingen, 1944), uric and phosphoric acids (Yant, Chornyak, Schrenk, Patty and Sayers, 1934), and a preponderance, even in venous blood, of the strong acid, CO-hemoglobin (Hastings, Sendroy, Murray and Heidelberger, 1924). All of these decrease the alkali reserve, thus forcing CO_2 out of the body by the respiratory pathway. This is accomplished evidently without great increase in ventilation. However, when the breathing stops terminally, the blood CO_2 rises rapidly because CO_2 cannot leave the body.

And at this point the blood acidity increases sharply from the increase in H_2CO_3, thus making for a terminal CO_2 excess.

In other papers (Swann and Brucer, 1949b, c), we have shown that the blood bicarbonate is inversely related to the blood lactic acid in anoxia. The same relationship was found to hold in CO-poisoning: the higher the lactic acid, the lower the $BHCO_3$. When the two variables were plotted against each other, one mE./L. of lactate was found to preempt 0.62 mE./L. of bicarbonate, approximately the same equivalence as found in dogs breathing 2.43 per cent O_2. The facct that all the lactate is not neutralized by $BHCO_3$ is a reflection of the participation of many other acids (see above) in the acidosis of CO-poisoning.

The pattern of respiratory change and acid-base equilibrium which we have discussed above is agreed upon by the vast majority of investigators. As a matter of fact, even Haggard and Henderson (1921) would agree with this statement for the most part: even though they insisted that "asphyxia causes not acidosis but alkalosis," they must have meant this statement to apply only to *early* and not to late asphyxia. They themselves state that acidosis occurs late in asphyxia (page 424): "Only during the terminal depression of breathing does a deviation . . . towards acidosis occur."

The behavior of the breathing in the complex events during CO-poisoning is to us a matter for some wry reflection: here in the organism are violent changes in blood O_2, in acidity, in pCO_2 and $BHCO_3$. All of these chemicals have been hailed as strong stimulators, if not exclusive controllers, of the pulmonary ventilation, and yet in spite of all these changes, the breathing continues regularly in these animals with only minimal changes. How may all of these changes be put together to predict breathing? No answer at present is possible.

It is generally recognized that in moderate CO-poisoning the pulse rate is accelerated, while in severe poisoning it is slow (Von Oettingen, 1944). In our experiment both effects are elegantly demonstrated: as the CO-saturation proceeds the heart rate first accelerates and then slows. Acceleration occurs with oxygen saturations from 80 to 30 per cent. Then, abruptly when the oxygen saturation reaches 10–12 per cent, a strong

bradycardia occurs. This is not by any means a sign of imminent heart failure, because the dogs' hearts continued beating vigorously for some 9 min. thereafter. Dogs breathing 2.43 per cent O_2 and dogs rebreathing through soda lime also show strong pulse slowing (Swann and Brucer, 1949b and c), but not of such great magnitude as in CO-poisoning. Thus, in the dogs breathing 2.43 per cent O_2, pulse rates below 50 appeared only once while the heart was still beating strongly, whereas in CO-poisoning, this rate appeared 6 times. The lowest rate observed was 15 beats per min. (dog No. II at 13 min.). In both types of anoxia, as death approached, the heart rate tended to speed up transiently with each expiration. Figure 2 in a previous paper (Swann and Brucer, 1949a) illustrates this phenomenon.

Low diastolic pressures and high systolic pressures accompanied the bradycardia. It is remarkable that in no instance in CO-poisoning after the O_2-saturation had fallen to 14 per cent did the diastolic pressure ever rise again above 100 mm. Hg. However, the systolic pressure often exceeded 300 mm. Hg after this point. A strong systemic vasodilation might be involved. If there were, one might expect that the venous pressure would rise. However, the measurements of effective venous pressure showed no conspicuous change, but were irregular and unpredictable. The fruitless nature of this measurement in our experience has been commented on in a previous paper (Swann and Brucer, 1949a), but for what it is worth, it does not indicate a systemic vasodilation in CO-poisoning.

Respiration failed, as shown in the data, at about the same time as the circulation failed. In fact, as we have pointed out, there is reason to believe that the respiration failed only *after* the circulation had essentially failed. This finding is contrary to most previous work. Drinker (1938) states, while discussing resuscitation: "After the breathing stops, one probably has, at the most, not more than 12 min. before artificial respiration must be applied, or the circulation will collapse and death will invariably ensue." We suspect (Swann and Brucer, 1949c) that this conclusion has been drawn primarily from experiments on anesthetized dogs, in which the respira-

tion does in fact fail long before the circulation. In the experiment of Von Oettingen, Donahue, Valaer and Miller (1941) for example, which dealt like ours with poisoning with 1 per cent CO, except that amytal was used, breathing stopped about 4 min. before circulatory failure. If unanesthetized animals are used, it appears to us highly probable that in either slow or rapid CO-intoxication, the breathing will be found to fail either after circulatory failure or simultaneously with it.

The fundamental damage in CO-poisoning has long been considered to be the damage caused by simple anoxia (Haldane, 1895), although many interesting dissents to this conclusion have been made (see Von Oettingen, 1944). Von Oettingen (1944) goes a step further in saying: "It may be stated that injury to the circulatory apparatus is the fundamental phenomenon of CO-poisoning and that most other sequelae may be explained on this basis." With this conclusion, as the foregoing discussion shows, we are in entire agreement (with the reservation that cerebral damage probably precedes cardiovascular damage). As we have pointed out, the most harmonious interpretation is that the circulation virtually fails before the breathing. There are several changes in the cardiorespiratory behavior, however, that appear at first glance to differ from the behavior in other types of anoxia, *i.e.*, breathing N_2 or 2.43 per cent O_2 or rebreathing through soda lime (Swann and Brucer, 1949a, b and c):

1. As discussed above, it is claimed that the blood pressure declines slowly all the way through CO-poisoning, whereas in the other anoxias it continues high until the heart abruptly fails. This claim appears to us based upon incomplete measurements only: the diatolic pressure does decline slowly, but the systolic pressure concurrently increases greatly. The cardiac output probably does not diminish until a short time before death.

2. One reaction of the heart to anoxia is a strong bradycardia; tachycardia appears only in mild anoxia and during circulatory failure (Swann and Brucer, 1949c). The bradycardia of CO-poisoning, however, is considerably greater than in the other anoxias, the difference being so pronounced that it tempts the observer to say that in this aspect CO-poisoning

differs in kind from the other anoxias. Another difference lies in the O_2-saturation at which the bradycardia appears: in CO-poisoning at 12 per cent whereas in progressive or acute anoxia it appears at about 30 per cent. Tentatively we are inclined to explain these differences on the same basis as the differences in respiratory behavior are explained: the heart rate is influenced not only by the O_2-saturation but by the O_2-tension as well. In CO-poisoning, with the peculiar situation of the O_2-saturation greatly reduced but the arterial O_2-tension normal, the cardiac reactions are different from the situations in which both saturation and tension are reduced.

3. Minor differences in electrocardiographic patterns in the two types of anoxia appear. Perhaps these also may eventually be ascribed to the same peculiar situation of O_2 carriage.

4. The changes in acid-base equilibrium in CO-poisoning, particularly those centering around the observed decreases in blood CO_2 (or $BHCO_3$ or combining capacity) have occasioned much research and discussion. Von Oettingen (1944) after reviewing the changes, suggests (p. 124): "it seems more likely that the decrease of reducible hemoglobin is responsible for this loss of CO_2", *i.e.*, the loss of CO_2 and alkali reserve. We are of the opinion that no peculiar changes in CO_2 carriage or in acid-base equilibrium occur, but that all of the observed changes may be readily fitted into the known patterns of change in the equilibrium, provided it is borne in mind that the breathing is only transiently and mildly stimulated in CO-poisoning. The behavior in CO-poisoning is best contrasted with the behavior in acute anoxia (breathing 2.43 per cent O_2) or progressive anoxia (rebreathing through soda lime). In these dogs, a respiratory and hematic alkalosis, with much "blowing off" of CO_2, occurred, followed by a metabolic acidosis. The acidosis was superimposed upon a point in the equilibrium well over on the alkaline side. Consequently, unless the dog lived for a long time, it died with a pH not far from normal, but with a lowered pCO_2 and blood bicarbonate. In dogs breathing CO, no respiratory alkalosis occurred because the breathing was only very mildly stimulated. The metabolic acidosis was then superimposed on the normal point in the

acid-base equilibrium and the animal finally died with a very low pH and also a lowered pCO_2 and $BHCO_3$. The metabolic acids in both cases preempted the alkali reserve and as well drove off CO_2, thus depressing both the pCO_2 and the $BHCO_3$. If the CO_2 carriage were deficient, one might expect the pCO_2 to rise; but it certainly does not rise, except terminally when the breathing has stopped. In summary, the blood pH in CO-poisoning is very low because the blood is carrying many metabolic acids plus CO_2; the blood pH in acute anoxia is close to normal because, although the blood is carrying about the same quantity of metabolic acids, it is carrying very little CO_2, this being continually washed out by overbreathing. Dogs No. I and II in the 2.43 per cent O_2 series Nos. III and IV in the rebreathing series are interesting exceptions to the above statement, in that they had very low pHs at death. The reason is evident: they are the long survivors; in the last few minutes of life their ventilation was as low as the ventilation in CO-poisoning, and with such a low ventilation their reactions are indistinguishable from the CO-poisoned dogs. In summary, all our observations are most harmonious with the hypothesis that the changes in CO-poisoning do not differ in kind from the changes in acute or progressive anoxia.

Summary

Simultaneous measurements are reported of the breathing, systolic and diastolic blood pressures, effective venous pressure, electrocardiograms, heart sounds, blood gases, pH, lactic acid, hemoglobin and plasma proteins of dogs, under local anesthesia, during anoxic death caused by breathing 1 per cent carbon monoxide in air.

Transient overbreathing was found to occur at blood oxygen saturations of about 30 per cent; the extent is so small as to be barely detectable, in contrast with other types of anoxia. In the same fashion as in acute or progressive anoxia, the breathing fails essentially as the circulation is failing; the cardio-respiratory failure is abrupt and not gradual. In fulminating, acute and progressive anoxia, circulatory failure takes place 2–5 min. after the arterial blood oxygen saturation falls to 12 per cent, but in carbon monoxide poisoning it takes place

about 9 min. after the oxygen saturation falls to 12 per cent. The changes in acid-base equilibrium are very similar to those in acute or progressive anoxia, differing only in that they occur in an animal that is not overbreathing.

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THE CARDIORESPIRATORY AND BIOCHEMICAL EVENTS DURING RAPID ANOXIC DEATH

V. OBSTRUCTIVE ASPHYXIA*

H. G. Swann and Marshall Brucer

All of the anoxic deaths studied in this series have dealt with situations in which the breathing was unhindered. The two following papers will describe fatal events in which free breathing is prevented: obstructive asphyxia and drowning.

Obstructive asphyxia is usually carried out experimentally by clamping the trachea or by obstructing a tracheal cannula. In everyday life it is not a common accident. Strangulation and throttling are exact equivalents to it. And certain types of "suffocation" are its equivalent, as in suffocation with a mouth gag or a garotte or with a blocked or iced face mask or with bed clothes. The "suffocation" of persons in a fire is obviously a different accident. The physiological changes during hanging are presumably in part the same as those in experimental obstructive asphyxia, except that the several spinal cord precludes resuscitation and undoubtedly modifies the reflex behavior. Except for the recent report of Allen, Echols, Hoeflich, O'Neal and Slocum (1947), which contrasts the asphyctic behavior of anesthetized and unanesthetized dogs, no comprehensive studies of the pattern of physiological change in obstructive asphyxia are available.

Methods

In asphyxiating the dogs, the animals were prepared under local anesthesia and all analyses were made as previously described (Swann and Brucer, 1949a). The asphyxiation was accomplished thus: a mask was made of pliable rubber sheeting in the shape of a truncated cone. Into the small end of the mask was fitted a 4 cm. section of brass tubing. After oiling

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the inside of the mask to prevent leakage, it was slipped over the dog's head. Meanwhile the dog could breathe unimpeded through the open brass tube. Obstruction was accomplished by inserting a rubber stopper into the open brass tube.

As will be shown, the dogs continued breathing movements until circulatory failure. We will give two characteristics of these movements, the rate and the strength, the latter being demonstrated by the lowest intrathoracic pressure observed during the movements. The two characteristics were measured only after they became readily apparent in the records and free from interfering movement, etc. Hence, measurements are shown in the tables only in the latter portion of the experiments. The changes in intrathoracic pressure resemble closely the changes shown in the records of any dog breathing deeply; Figure 1 in a pervious paper illustrates this type of movement (Swann and Brucer, 1949a).

Results

The results are shown in Tables I, II, III and IV. Figure 1 illustrates the changes in one dog, No. II.

Rhythmic breathing movements continued right through to circulatory failure, ceasing in 3 out of the 4 dogs only when the blood pressure had fallen to about 25/15. They were strong in quality, measuring, right up to the end, 50–100 cm. H_2O of negative pressure. The animals continued to make violent struggles or to have convulsions even up to the point of heart failure.

The dogs survived 7–14 min. The cause of the relatively long survival of dog IV probably lies in a technical defect in this one experiment. The stopper was placed in the mask of the dog at zero time just after the dog had inspired. This allowed the dog to rebreathe in and out of the mask a volume of air estimated to be roughly 300 cc.—enough presumably to postpone death to 14 min. Arterial O_2-saturations fell progressively; the dogs' hearts failed about 2 min. after the O_2-saturation had fallen below 10 per cent.

The CO_2-content first rose rapidly, reaching a peak of 56 vols. per cent about a third of the way through the experiment. Then, with the blood lactate starting to increase, the CO_2-

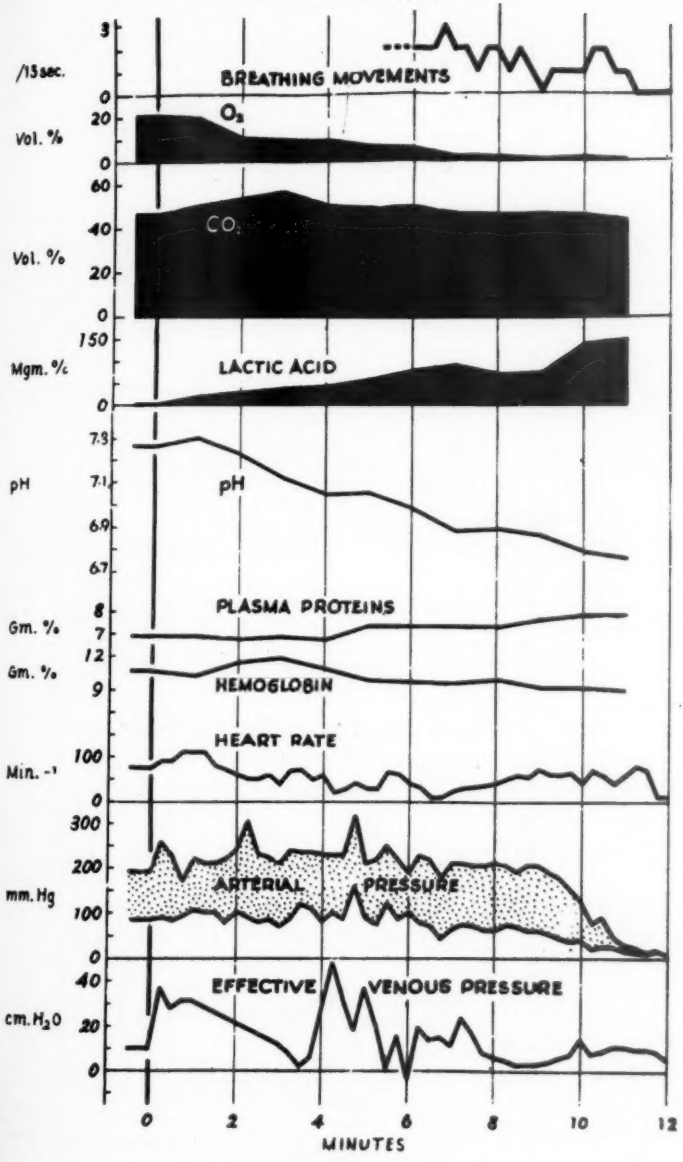

FIGURE 1
Course of obstructive asphyxia. Dog No. II.

TABLE I

Obstructive Asphyxia
Adult Female, 7.5 Kg.

Minutes	Breathing movements per minute	Lowest intrathoracic pressure, cm. H_2O	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic / Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0			18.9	89	43.1	46	21	0	7.29	15.8	8.5	75	216/101	115	—2	—5
1			19.2	95	51.4	60	24	40	7.23	14.9	8.2	50	260/91	169	87	24
2	5	—80	5.3	24	52.4	67	25	50	7.19	16.0	7.7	42	283/150	133	24	0
3	7	—64	6.7	30	57.4	81	27	0	7.14	16.3	7.7	42	264/92	172	19	—1
4	8	—72	11.4	51	52.8	78	24	0	7.11	16.5	7.7	35	238/47	191	16	—4
5	9	—110	2.1	9	48.8	83	23	45	7.06	17.5	7.7	58	240/72	168	13	—3
6	12	—94	8.4	40	56.6	105	25	70	7.01	15.4	8.2	72	196/56	140	14	—3
7	0	0	1.7	8	42.2			85			7.3	30	40/18	22	15	0
8	0	0	0.8	2	44.7	99	20	70	6.92		7.1	11	3/3	0	6	—4

TABLE II

Obstructive Asphyxia

Young Adult Female, 8.0 Kg.

Minutes	Breathing movements per minute	Lowest intrathoracic pressure, cm. H_2O	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0			20.6	100	46.9	49	20	0	7.21	10.7	6.9	75	191	85	106	10	4
1			19.1	100	50.5	49	24	20	7.30	10.3	6.9	110	220	107	113	31	10
2			10.3	66				30	7.23	11.5	6.8	60	242	102	140		
3			10.0	62	56.3	80	25	40	7.12	11.9	6.9	36	210	72	138	12	0
4			9.8	65	50.8	83	23	45	7.05	11.0	6.8	59	232	83	149	6	0
5			7.0	52	49.6	79	22	60	7.06	10.0	7.4	30	210	92	118	37	—2
6	8	—62	5.8	44	49.7	91	21	80	6.99	9.8	7.4	39	190	102	88	—4	—6
7	8	—24	2.4	18	46.8	105	19	90	6.89	9.7	7.4	23	210	64	146	11	—4
8	8	—33	2.1	15	46.2	101	19	70	6.90	10.0	7.4	41	212	63	149	6	—2
9	2	—78	1.0	8	46.6	107	19	75	6.87	9.3	7.7	72	206	63	143	3	—2
10	6	—70	2.0	16	46.1	122	19	140	6.80	9.3	7.9	42	129	40	89	14	5
11	3	—46	1.0	8	43.5	122	18	150	6.77	9.1	7.9	60	32	20	12	11	0
12	0	0										11	12	10	2	5	0

TABLE III

Obstructive Asphyxia

Adult Female, 8.8 Kg.

Minutes	Breathing movements per minute	Lowest intrathoracic pressure, cm. H_2O	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0			18.0	85	44.1	37	22	0	7.40	15.5	6.5	160	190/91		99	—3	—4
1			8.1	45	47.1	58	27	0	7.28	13.4	6.2	47	254/97		157	34	6
2	6	—36	7.2	40	49.5	52	24	60	7.28	13.2	6.5	45	297/100		197	4	—7
3	6	—47	7.4	36	53.3	68	23	60	7.15	15.3	6.5	48	316/79		237	—1	—10
4	11	—48	3.1	14	50.8	85	24	75	7.06	15.8	6.7	80	284/110		174	0	—9
5	8	—70	2.4	12	47.9	86	22	65	7.03	15.0	6.8	46	180/51		129	4	—7
6	7	—79	1.6	8	45.2	82	20	85	7.02	15.0	6.8	80	125/37		88	2	—8
7	2	—32	1.6	7	47.8	84	21	95	7.01	16.0	7.0	90	23/18		5	5	—3
8	0	0	1.4	7	41.2	85	19	100	6.96	14.7	6.5	0	6/6		0	5	—3

TABLE IV

Obstructive Asphyxia
Adult Female, 7.4 Kg.

Minutes	Breathing movements per minute	Lowest intrathoracic pressure, cm. H_2O	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0			21.7	100	42.8	51	20	0	7.21	15.4	6.7	81	209	80	129	3	—3
1			18.4	98	44.1	51	21	0	7.23	14.4	7.2	80	220	97	123	18	4
2			19.7	100	50.2	61	23	0	7.20	13.2	6.8	66	197	75	122	27	8
3			11.3	62	53.5	71	25	0	7.16	14.0	6.3	69	317	91	226	61	1
4			12.2	66	56.8	81	26	0	7.13	14.2	7.3	34	272	97	175	33	6
5	3	—38	6.7	33	53.7	83	25	32	7.10	15.7	7.2	32	350	92	258	23	1
6	4	—38	5.9	30	50.5	75	23	40	7.10	15.3	7.2	34	327	70	257	22	2
7	4	—48	4.2	22	50.9	99	22	53	6.98	14.8	7.2	50	260	73	187	13	0
8	4	—36	3.6	17	48.7	118	20	80	6.87	16.2	7.0	95	218	76	142	13	0
9	6	—45	2.4	12	44.8	124	20	125	6.80	15.4	7.0	62	191	40	151	14	2
10	5	—43	3.8	19	40.0	120	17	130	6.75	15.1	7.2	55	235	45	190	16	3
11	6	—47	2.4	12	39.8	128	17	175	6.71		7.3	50	184	35	149	16	4
12	6	—54	4.6	20	41.2	141	18	170	6.69	17.5	8.1	85	236	47	189	14	3
13	8	—50	1.9	10	37.6	145	16	170	6.61	15.2	7.3	63	132	28	104	12	2
14	5	—12	1.5	8	37.5	140	15		6.62	14.0	8.1	65	11	8	8	14	3
15	0	0										36	3	3	0	9	2

content fell, until at death it was the same or less than the initial content. The blood bicarbonate rose slightly at the start and then remained constant until the blood lactic acid started to rise. It then decreased in direct proportion to the lactic acid increase. The CO_2-tension rose consistently throughout the experiment; terminally it reached very high levels. In dog No. IV which was rebreathing a small volume of gas (see above), it came to a maximum of 145 mm. Hg. Meanwhile the dogs slowly progressed into an extreme acidosis: No. IV had the lowest pH in all the experiments on fatal anoxia, *i.e.*, 6.61 at the 13th min.

The heart rate followed a typical pattern: within 90 sec. there occurred a strong slowing. The heart rate then remained slow except for terminal flurries of tachycardia when approaching death. The slow rate was accompanied with a great elevation in systolic pressure and a fall in diastolic pressure. Heart failure occurred very abruptly, with the pulse pressure dropping from 100 to about 10 mm. Hg within a single minute.

The P waves in the electrocardiograms became irregularly dissociated from the ventricular complexes with the early bradycardia. They reappeared when the heart transiently accelerated and then disappeared when the heart slowed. Shortly before systolic collapse the P waves usually inverted and became completely dissociated in a complete block, following which they disappeared until long after systolic collapse. Ventricular complexes were similar to those occurring in rebreathing, *i.e.*, low voltage R waves and high ST segments slurring into high T waves. Ventricular fibrillation did not occur in any dog. Toward the end of the experiments, long after systolic collapse, there was a tendency for the R and T waves to fuse in a single monophasic complex. The last discernible complexes appeared at 20–23 min., about 12 min. after heart failure.

The second heart sound disappeared about a minute before the first heart sound; the latter disappeared when the blood pressure had fallen to about 50/20.

Discussion

The 8 odd minutes of survival of these dogs contrasts sharply with the 5 minute survival of dogs breathing N_2 (Swann and

Brucer, 1949a). The difference lies in the rate of oxygen desaturation: when breathing N_2, the dogs actually "blow off" oxygen, reducing their oxygen content to the vanishing point at about 1 min. The asphyxiated dogs, unable to expire, consumed all available oxygen before dying. Man probably survives about the same time in complete obstructive asphyxia; MacFall (1925) shows some pulse records taken on hanged men; arterial pulsations became imperceptible at 12–14 min.

The exceedingly low pH of the dogs' bloods in this experiment is matched by those reported for pigs in long-sustained acute anoxia by Koehler, Behneman, Benell and Loevenhart (1925). In fact, such pHs actually go below the isoelectric point for some of the body proteins, *e.g.*, hemoglobin and serum globulin (Hawk, Oser and Summerson, 1947). But in spite of this, in the experiments of Koehler, Behneman, Benell and Loevenhart (1925), the breathing continued and recovery occurred readily when the anoxia was terminated.

The acid-base equilibrium changes represent the acidosis of a CO_2-excess combined with a metabolic acidosis. The dogs, unable to exhale CO_2, at first show a rise in CO_2-content and in blood bicarbonate. But then when the blood lactate starts to rise, the strong acid, lactic, displaces the weak acid, carbonic, from its base, causing a fall in the blood bicarbonate and the CO_2-content. Both acids profoundly depress the pH. The pCO_2 continues to rise. Probably CO_2 is driven far back in the tissues.

In this experiment, the blood bicarbonate decreased as the blood lactate acid increased, just as in the previous types of anoxia. After plotting this relationship, it was found that on the average each mE./L. of lactic acid preempted 0.44 mE. of $BHCO_3$. This is considerably lower than the values found for the simple anoxias and CO-poisoning, for they ranged from .6 to .8 mE./L. of bicarbonate preempted. It is apparent that some other acid besides lactic must be present in large quantities in obstructive asphyxia, and that acid obviously is H_2CO_3, formed from the CO_2 that cannot be exhaled.

The early strong bradycardia is of interest in that it occurs before the dogs become very anoxic. Hitherto in our experiments this vagal-controlled bradycardia has always been asso-

ciated with an arterial oxygen saturation of 30 per cent or less but in obstructive asphyxia it occurs long before this degree of desaturation is reached. In dog No. III, it was particularly rapid: from a rate of 160 per min. at the start, it dropped to 112 at 15 sec., 88 at 30 sec. and 58 at 45 sec. Cardiac acceleration was found in only one dog (No. II) and even here it was only a transient acceleration. At no place in our experiments is the evidence so clearly against the general conclusion that anoxia (and asphyxia) cause acceleration of the heart beat (see Swann and Brucer, 1949c). In this experiment, it is only when the circulation is failing that a short period of irregular cardioacceleration occurs. Undoubtedly these dogs' adrenal medullas were violently stimulated by the asphyxial situation, yet the chronotropic action of adrenalin was completely overborne by vagal inhibition.

Summary

Simultaneous measurements are reported of the breathing movements, systolic and diastolic blood pressures, effective venous pressure, electrocardiograms, heart sounds, blood gases, pH, lactic acid, hemoglobin and plasma proteins of dogs, under local anesthesia, during the anoxic death caused by obstructive asphyxia.

The dogs survived about 8 minutes in contrast with the 5-minute survival of dogs breathing nitrogen, an effect considered due to "blowing-off" of oxygen by dogs in nitrogen anoxia. Carbon dioxide tensions were observed as high as 145 mm. Hg and pHs as low as 6.61. The main reaction of the heart was a bradycardia, with tachycardia appearing only terminally as the circulation was failing. Breathing movements continued strong until the circulation failed.

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THE CARDIORESPIRATORY AND BIOCHEMICAL EVENTS DURING RAPID ANOXIC DEATH

VI. FRESH WATER AND SEA WATER DROWNING*

H. G. Swann and Marshall Brucer

A preliminary report (Swann, Brucer, Moore and Vezien, 1947) has been made on the terminal events in drowning. In that report detailed data from two dogs was given, one drowned in salt water and one drowned in sea water. This report will serve only to present the full data of the experiment. We will not repeat here the description of the technics used nor the discussion of the results, but will present only the data obtained on all nine dogs studied, and add a description of the changes in breathing movements and electrocardiograms.

Subsequent to the preliminary report, it was found that the Gulf of Mexico sea water used in these experiments was relatively dilute. As Table X shows, its salt content was 23.81 g./L. or about 69 per cent of the salinity of open ocean water. This fact in no way invalidates any of our previous work; if the drowning occurred in open ocean water, probably the hemoconcentration caused by the inhaled sea water would be of greater magnitude than reported here, because ocean water, being more saline, exerts a stronger osmotic pressure than gulf water.

Results

The changes in 5 dogs drowned in fresh water and 4 dogs drowned in sea water are shown in Tables I through IX[1]. Figures 1 and 2 illustrate the changes in No. IV (fresh water) and No. VI (sea water).

Table IV is the same as Table I of the previous report. The early table is in error in one respect: the whole blood

*From the Carter Physiological Laboratory, The University of Texas Medical Branch, Galveston. These papers report a portion of the results obtained in a program of research on the efficacy of resuscitation procedures. The program is sponsored by the Air Materiel Command, Wright Field, Ohio, under contract No. W 33-038 ac-14379. Received for publication July 6, 1049.

[1]The dogs have been re-numbered as follows: No. I (and Table I) corresponds to No. 70 of the previous report, II to 72, III to 74, IV to 76, V to 128, VI to 82, VII to 84, VIII to 86, and IX to 136.

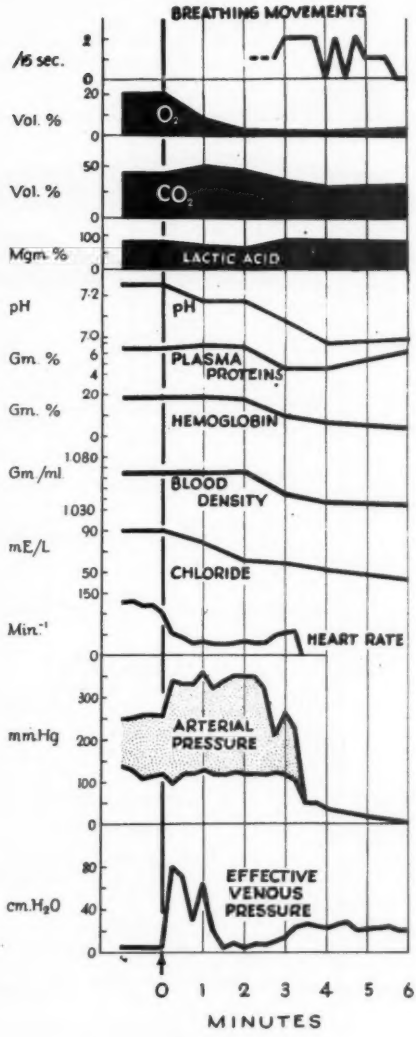

FIGURE 1

Course of fresh water drowning. Dog No. IV.

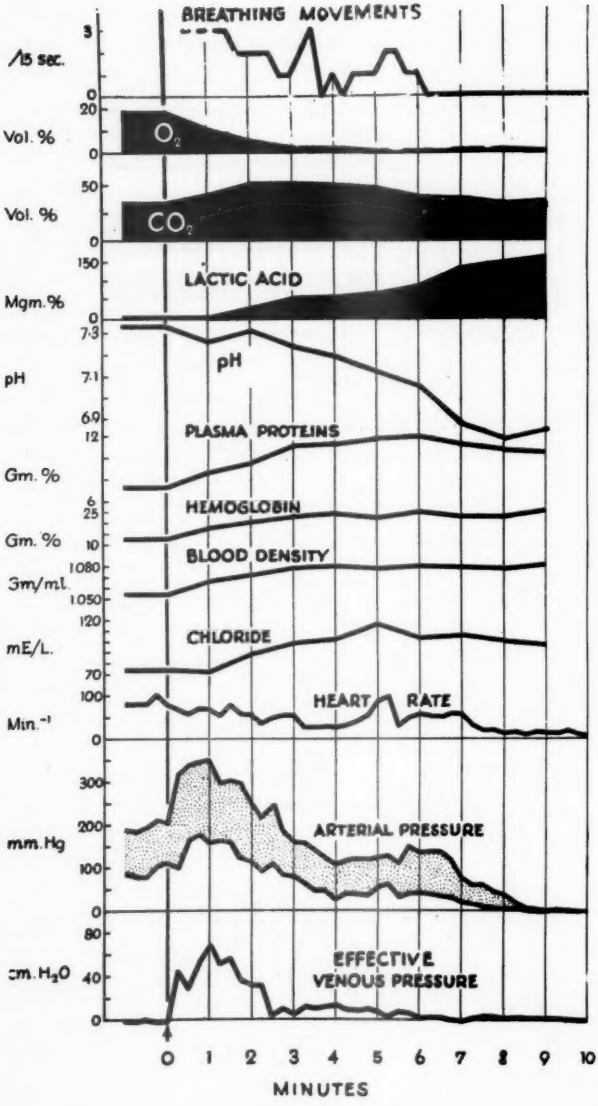

FIGURE 2
Course of sea water drowning. Dog No. VI.

TABLE I

Fresh Water Drowning
Young Adult Male, 6.5 Kg.

Minutes	Breathing movements per minute	Lowest intrathoracic pressure, cm. H_2O	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic / Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0			18.8	100	37.5	46	18	60	7.21	12.5	7.7	132	84/47	37	—3	—2
1			8.5	46	42.0	58	18	60	7.10	13.7	8.3	32	244/64	180	24	0
2	5	—64	4.1	27	36.2	88	15	75	6.86	11.2	6.7	18			22	—1
3	6	2	1.8	21	24.3	62	10	90	6.81	6.2	4.9	40	70/37	33	68	20
4	0	0	2.8	100	20.8	63	6	80	6.70	1.3	6.1	48*	24/24	0	32	9
5	0	0											13/13	0	31	11

*Ventricular fibrillation at 3:30, succeeded at 3:58 by a reappearance of venous pulse waves, but only very irregular electrocardiographic complexes.

TABLE II

Fresh Water Drowning

Young Adult Male, 7.0 Kg.

Minutes	Breathing movements per minute	Lowest intrathoracic pressure, cm. H_2O	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0			7.3	89	37.1	38	16	62	7.25	6.0	6.3	160	268	93	175	14	4
1			5.2	63	41.8	51	18	63	7.17	6.0	6.3	47	295	86	209	40	8
2			5.5	100	41.5	54	18	73	7.13	3.7	5.2	70	252	82	170	18	—4
3	9	—28	2.0	29	33.7	56	14	80	7.02	5.1	4.8	73	160	42	118	23	—2
4	9	—26										65	30	20	19	36	6
5	7	—26	2.8	40	30.5	62	13	76	6.93	4.8	6.5	50	16	4	0	32	7
6	0	0										70	9	9	0	35	6

TABLE III

Fresh Water Drowning
Young Adult Female, 8.0 Kg.

Minutes	Breathing movements per minute	Lowest intrathoracic pressure, cm. H_2O	Arterial O_2, vols. %	Arterial O_2-saturation %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic / Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0			20.7	100	30.8	31	14	58	7.29	14.1	7.0	130	250/130	120	6	0
1			12.0	63	44.0	50	21	55	7.24	14.1	7.0	25	295/85	210	47	9
2			8.4	42	50.5	58	24	54	7.24	14.6	7.4	28	314/101	213	36	3
3			5.1	26	45.1	50	17	58	7.15	14.4	6.8	22	295/88	207	26	0
4	3	—39	2.5	13	44.0	65	20	62	7.11	13.8	6.5	39	324/112	212	19	—5
5	0	0	2.8	22	34.6	65	15	58	6.98	9.2	5.3	39	207/82	125	27	—5
6	6	—47	2.2	24	34.5	79	14	54	6.88	6.8	5.1	*	—/10	0	41	6
7	0	0	1.0	8	35.1	83	15	56	6.87	9.5	5.4					

*Ventricular fibrillation at 5:39.

TABLE IV

Fresh Water Drowning

Adult Female, 7.0 Kg.

Minutes	Breathing movements per minute	Lowest intrathoracic pressure, cm. H_2O	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0			21.0	82	43.6	53	23	8	7.24	18.8	6.5	123	254	120	134	5	0
1			8.5	33	51.3	72	25	70	7.16	18.8	6.8	34	362	128	234	38	15
2			3.8	16	47.3	69	24	65	7.16	17.2	6.7	34	350	120	230	7	—14
3	6	—60	2.8	21	37.9	61	17	89	7.06	9.7	4.7	56	267	118	149	22	—4
4	5	—24	2.5	26	31.7	62	13	89	6.95	7.1	4.6	*	—/35		0	25	—4
5	5	—76											—/23		0	21	—8
6	0	0	4.1	79	33.2	61	13	82	6.97	3.8	6.2		—/12		0	23	—2

*Ventricular fibrillation at 3.29.

TABLE V*

Fresh Water Drowning
Adult Female, 10.0 Kg.

Minutes	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic / Diastolic	Pulse pressure, mm. Hg	Venous pressure, cm. H_2O
0	20.2	94	41.9	35	20	7.39	15.8	7.3	80	280/142	138	4
1	5.9	31	50.4	50	24	7.30	13.8	7.0	60	404/195	209	63
2	4.0	19	47.0				15.4	6.9	62	387/168	219	19
3	10.0	63	39.5	50	18	7.18	11.7	4.5	98	215/136	79	30
4	3.0	21	35.4	45	16	7.17	10.3	4.9	6	56/40	16	30
5										20/16	4	28

*In this experiment, no measurements were obtained on breathing movements, lactic acid, chloride or intrathoracic pressure.

TABLE VI

Sea Water Drowning
Adult Female, 9.7 Kg.

Minutes	Breathing movements per minute	Lowest intrathoracic pressure, cm. H_2O	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic / Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0			18.4	100	34.8	34	18	0	7.34	13.0	7.3	81	213/102	111	—1	—5
1			11.2	46	42.0	47	19	0	7.27	17.8	8.7	68	360/167	193	70	7
2	9	—56	6.2	22	52.6	54	27		7.32	20.8	9.6	58	255/121	134	35	—4
3	6	—34	3.2	10	52.7	59	25	53	7.25	23.2	11.1	57	166/80	86	12	—8
4	3	—21	2.9	9	51.5	70	27	55	7.20	24.4	11.2	30	114/30	84	13	—7
5	5	—53	1.3	4	49.1	76	25	65	7.13	22.8	11.8	84	130/62	68	6	—7
6	2	—16	1.1	3	41.2	79	22	86	7.06	25.5	12.0	58	142/47	95	4	—6
7	0	0	1.6	5	39.0	98	18	133	6.88	23.1	11.3	59	84/27	57	2	—8
8	0	0	1.7	6	34.7	98	16		6.81	23.0	10.8	17	48/18	30	3	—8
9	0	0	1.1	3	36.8	98	17	163	6.85	25.4	10.6	15	18/8	10	2	—8
10	0	0	1.3	4	35.7	97	17	163	6.85	25.0	11.8	10	9/9	0	1	—8

TABLE VII*

Sea Water Drowning
Adult Male, 8.0 Kg.

Minutes	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic / Diastolic	Pulse pressure, mm. Hg	Venous pressure, cm. H_2O
0	19.0	100	37.2	34	18	55	7.35	13.2	7.4	55	211/100	111	16
1	5.2	27	62.3	72	29	56	7.23	14.0	7.7	37	314/91	223	66
2	3.2	10	58.7	80	31	56	7.20	23.5	7.3	37	168/53	115	10
3	1.9	6	52.7	82	27	65	7.13	24.4	7.2	57	119/30	89	10
4	1.4	4	49.7	93	25	70	7.04	24.4	7.3	59	118/40	78	10
5	1.4	4	47.5	106	23	81	6.92	24.4	7.3	72	57/27	30	9
6	1.9	5	51.1	112	25	96	6.91	24.9	7.3	60	10/7	3	11
7	2.3	7	45.5	98	23	87	6.96	25.1	7.3	30	7/7	0	11

*In this experiment, no measurements of the breathing movements or intrathoracic pressure were obtained.

TABLE VIII*

Sea Water Drowning

Adult Female, 7.5 Kg.

Minutes	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic / Diastolic	Pulse pressure, mm. Hg	Venous pressure, cm. H_2O
0	18.2	98	38.7	46	18	0	7.21	13.5	7.6	100	240/100	140	18
1	7.2	33	51.2	51	25	79	7.31	16.0	8.9	60	315/142	173	53
2	5.7	21	58.6	80	29	56	7.18	20.0	11.3	35	204/84	120	9
3	2.5	9	59.6	99	29	54	7.07	20.9	11.9	30	147/35	112	11
4	2.5	9	54.8	65	22	54	7.15	19.8	12.5	31	145/40	105	10
5	1.1	4	54.7	90	25	78	7.07		11.9	55	89/30	59	7
6			58.8	96	28	87	7.07	18.5	11.6	58	28/10	18	8
7										58	8/8	0	8

*In this experiment, no measurements of the breathing movements or intrathoracic pressure were obtained.

TABLE IX

Sea Water Drowning
Adult Female, 9.6 Kg.

Minutes	Breathing movements per minute	Lowest intrathoracic pressure, cm. H_2O	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0			15.9	86	38.5	40	18	0	7.28	13.6	6.3	68	239	136	103	1	—9
1			10.4	54	44.1	53	21	0	7.21	14.2	6.5	48	322	168	154	47	14
2			6.7	28	52.9	61	26	0	7.25	17.6	9.5	62	255	138	117	15	—2
3	3	—55	3.4	14	54.5	70	26	40	7.19	17.6	10.2	50	161	68	93	8	—3
4	7	—57	4.2	15	59.1	96	28	62	7.07	20.0	10.2	24	128	43	85	14	0
5	8	—58	1.8	7	50.3	86	23	70	7.05	18.0	11.9	32	111	38	73	14	1
6	8	—39	2.5	9	47.2	97	23	70	6.99	21.7	11.8	21	94	9	85	14	2
7	0	0	1.8	6	41.1	73	21	87	7.07	23.1	12.0	65	96	33	63	11	2
8	0	0			42.5	97	23	95	6.94	24.4	11.2	56	52	18	34	12	2
9	0	0			42.7	101	21	157	6.89	22.4	10.6	11	51	9	42	13	2
10	0	0										10	27	8	19	13	2
11	0	0										8	15	10	5	9	2

TABLE X

Composition of Sea Water

	Na	K	Ca	Mg	Cl	SO_4	HCO_3	Total
Galveston, g./L.	13.51	1.87	.12	6.69	.34	.30	.98	23.81
Open ocean, g./L.* ..	18.98	2.65	.14	10.56	.38	.40	1.27	34.38

*From Sverdrup, Johnson and Fleming (1942).

density at zero time should be 1.0658 instead of 1.0734 and the hemoglobin content of the same sample should be 18.8 instead of 22.5. This change will make the slope of the curve of Figure 2, dog 76, less in its initial stages and will change the value of "water diluting" (last column of Table II) for dog No. 76 from 1.2 to 0.97. Table VII is the same as Table III of the first report. All pHs have been recomputed to the pH of 38° instead of the pH of room temperature as shown in the first report on drowning.

In the tables are shown several data not included in the first report. The breathing movements, as registered by the intrathoracic cannula are characterized with respect to frequency and strength. These movements were present in all dogs; they had the same characteristics as the breathing movements in obstructive asphyxia. In fresh water drowning, they continued, in 3 out of the 4 dogs which experienced ventricular fibrillation, after the heart had fibrillated. In sea water drowning, they continued through the sixth minute.

The tables also show the arterial O_2-saturation. Because of the violent hemodilution occurring, the computed O_2-saturation shows an increase in several cases, *i.e.*, to 100 per cent in No. II. This, of course, is only an apparent increase, for the O_2-content shows that the blood O_2 is actually very low. The CO_2-tensions were not greatly elevated in fresh water drowning, but, as in obstruction asphyxia, they became very high in salt water drowning. The difference is unquestionably due to the fact that the blood CO_2, although accumulating during fresh water drowning, was so diluted by the ingress of water that it did not actually increase.

Violent hemolysis occurred in all dogs during drowning, being particularly strong in the blood samples drawn late in the

experiment. Thus, at the fifth or sixth minute, the plasma of dogs II and V contained 3.6 and 2.8 g. per cent hemoglobin respectively.

Early in the experiment in fresh water drowning, the electrocardiograph showed a dissociation of auricular and ventricular complexes with the concommitant bradycardia. The P waves then appeared and disappeared irregularly, followed, at the time of systolic collapse, by the appearance of waves similar to those of auricular fibrillation. In 4 dogs the final complexes, appearing 18–22 min. after systolic collapse, appeared to be P waves. The changes in ventricular complexes began with an increase in the amplitude, sometimes with inversion, and later reversion, of T waves. There then began a gradual elevation of the ST junction. The duration of the QT interval gradually lengthened and the ST segments climbed higher. The R wave amplitude increased, while that of the T wave decreased until the QT complexes became a monophasic wave. In 3 or 5 dogs a negative wave then developed at the end of T and the dogs proceeded into ventricular fibrillation. In dog No. I ventricular fibrillation reversed and was followed at 7 min. by solitary ventricular monophasic beats. In the only dog now showing ventricular fibrillation, the QRST wave became monophasic and less frequent towards the end.

In the electrocardiograms of dogs during sea water drowning, P waves disappeared almost immediately and then returned about 1–2 min. after the start. The PR interval lengthened until there was a dissociation of auricular and ventricular complexes with partial and complete blocks. Shortly thereafter the P waves reappeared as normal waves until just before systolic collapse. Following collapes they appeared irregularly. The R waves decreased in amplitude very early; the T waves then inverted. Shortly before collapse T waves became upright, the ST segment developed a slightly higher take-off; and then fused with a low voltage T. Complexes disappeared at about 20 min., except for one dog—No. VII—in which they continued until 42 minutes.

When ventricular fibrillation occurred, the second sound disappeared only a few seconds before the first sound. The second heart sound disappeared about 30 seconds before the

first sound in sea water drowning. The first sound disappeared when the systolic pressure was 10–20 mm. Hg.

SUMMARY

Simultaneous measurements were made of the breathing movements, systolic and diastolic blood pressure, effective venous pressure, electrocardiagrams, heart sounds, blood gases, pH, lactic acid, hemoglobin and plasma proteins in dogs during fresh water and sea water drowning.

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THE CARDIORESPIRATORY AND BIOCHEMICAL EVENTS DURING RAPID ANOXIC DEATH

H. G. Swann and Marshall Brucer

VII. EXSANGUINATION*

The terminal physiological events in exsanguination or in severe hemorrhage have been studied many times. Recently in especial, the Russian group under Negovski (1945–1946) has carefully examined many aspects of the physiology of rapid exsanguination. All the studies, with only one exception known to the authors, were made under general anesthesia; ether (Cannon and Cattell, 1922; Roome, Keith, and Phemister, 1933; Coonse, Foise, Robertson, and Anfranc, 1935; Negovski, 1945–1946), or urethane (Aub and Cunningham, 1920; Doi, 1921), or barbiturates (Johnson and Blalock, 1931; Roome, Keith, and Phemister, 1933; Coonse, Foise, Robertson, and Anfranc, 1935; Lehman and Amole, 1938). Frequently, morphine is also employed (Wiggers, 1942; Negovski, 1945–1946). Wiggers (1942), discussing the anesthetics best used in studying shock, recommends chloralozane or morphine-barbiturate anesthesia. The one exception, in which only novocain anesthesia was employed is described by Coonse, Foise, Robertson, and Anfranc (1935) but no data are given on their experiments on dogs so anesthetized. Since all general anesthetics strongly influence the course of hemorrhagic shock, we have reinvestigated the problem employing local anesthesia only.

The effects of hemorrhage are well recognized (Cannon, 1923; Wiggers, 1923; Harkins, 1941; Moon, 1942; Wiggers, 1942; Negovski, 1945–1946) and so will not be reviewed until our own results are discussed below.

Methods

All analyses and measurements were made as described in a previous paper (Swann and Brucer, 1949a). Arterial blood

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was drawn out of a cannula in the femoral artery at a rate of roughtly 1.7 ml. per kilogram of body weight per minute. The blood was drawn in small samples, every minute or every two minutes, over a period of about 10 seconds. The actual times for each sample and cumulative volume withdrawn from each dog are shown in Figure 1. The four rates were, re-

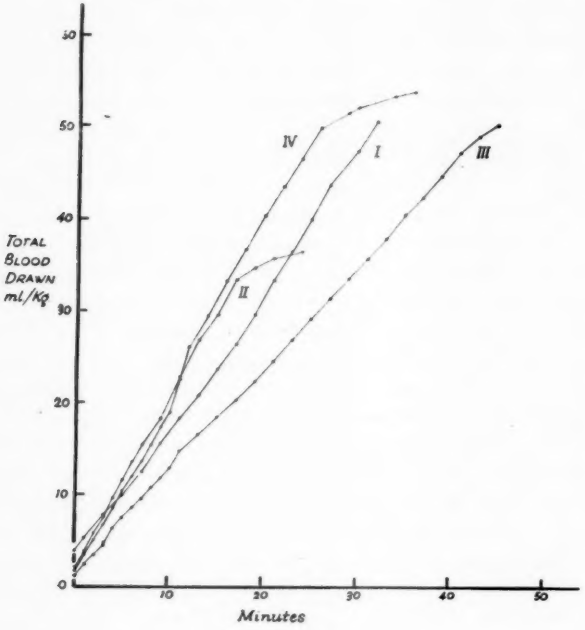

FIGURE 1

Rate of hemorrhage.

spectively, 1.6, 2.0, 1.2, and 2.0 ml. per kg. min. It will be noted that blood was drawn from dogs II and IV almost twice as fast as from dog III.

RESULTS

Tables I, II, III, and IV show the results; one protocol, that of dog No. II, is shown in graphic form in Figure 2.

TABLE I

*Exsanguination**

Adult Female, 6.1 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2–saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure: Systolic	Arterial blood pressure: Diastolic mm. Hg	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.50	2.0	3.5	15.7	86	38.9	42	16	0	7.21	13.4	6.8	105	216	116	100		
4	.55	2.2	6	16.3	84	37.3					14.2	6.9	110	221	116	105		
10	.50	2.1	5	16.8	94	33.5	36	16	0	7.26	13.1	6.5	104	214	125	89		
14	.65	2.7	10						0	7.26	13.0	6.4	170	160	116	44		
18	.90	3.7	7	15.3	94	31.0	37	14	20	7.20	12.0	6.3	118	105	60	45	18	7
21	.57	2.3	6										98	86	46	20	—1	—3
24	.42	1.7	6	15.6	99	23.7	27	11	67	7.22	11.6	6.9	102	59	38	32	1	—1
30	.90	3.8	5.5	13.1	89	14.6	17	7	115	7.21	10.8	7.2	130	40	25	22	1	—1
32	1.04	4.3	7							7.10			130	40	25	23	—3	—2
35	.15	.6	4						150	7.06	10.5	8.1	120	37	19	22	—6	—4
38	.22	.9	4	12.6	93	12.1	21	6	165	7.03	10.0	8.2	125	38	19	14	—1	—2
42	.17	.7	3							6.95			50	17	11	3	—9	—10
43	0		0										50	13	10	1	—9	—10

*Blood was drawn at a rate of 1.6 ml./Kg./min.; see Fig. 1. 350 ml. were withdrawn, amounting to 5.7% of the body weight.

TABLE II

*Exsanguination**

Young Adult Female, 5.5 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2-saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure mm. Hg: Systolic	Arterial blood pressure mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	1.00	4.5	3	14.6	82	31.9	42	15	0	7.16	13.2	6.4	69	155	82	73		
2	.28	1.3	4	15.6	92	32.0	43	15	0	7.17			121	137	80	57		
4	.30	1.4	4	15.7	96	30.7	35	13	0	7.19	12.0	6.1	192	123	76	47		
6	.40	1.8	5	16.0	98	29.3	32	14	0	7.25	12.0	6.2	170	100	58	42		
9	.23	1.0	5	14.3	92	29.3	39	14	0	7.16	11.5	5.9	120	64	27	37	—6	—5
13	.30	1.4	6	14.0	93	24.5	29	12	65	7.21	11.2	6.4	121	60	30	30	—10	—8
17	.10	.5	3	13.6	97	26.9	36	12	115	7.14	10.3	5.8	115	43	22	21	—11	—7
21	0	0	0						80	7.20		6.8	8	48	9	41	—8	—6
22	.22	1.0	3										21	26	6	17	—8	—6
25	0		0										99	15	7	8	—8	—5

*Blood was drawn at a rate of 2.0 ml./Kg./min.; see Fig. 1. 201 ml. were drawn, or 3.7% of the body weight.

TABLE III

*Exsanguination**

Adult Male, 11.3 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	.64	1.7	3	20.1	96	45.0	54	22	0	7.22	15.4	6.2	135	132	90	42		
8	.67	1.7	3							7.27	14.5	6.1	165	93	54	39		
11	.60	1.5	3			44.3	47	21	0	7.28	15.2	5.7	170	73	36	37	0	—5
23	1.17	3.0	4.5			41.6	41	21	30	7.32	14.8	5.5	190	71	35	36	—1	—5
26	1.32	3.4	5										199	54	27	27	—2	—5
31	1.60	4.1	3.5			32.2	31	16	92	7.32	13.5	5.6	195	46	26	21	0	—4
35	2.14	5.5	5.5							7.29			200	27	11	18	—1	—3
39	.85	2.2	4.5			21.4	28	10	208	7.16	12.4	6.2	205	36	17	22	1	—2
43	.63	1.6	3	21.1	100	26.4	39	12	195	7.10	12.3	6.2	179	27	9	16	—2	—4
45	.77	2.0	3										90	15	5	7	—3	—5
46	.05		3										60	8	2	6	—4	—5
47	0		0										60	4	2	1	—6	—8

*Blood was drawn at a rate of 1.2 ml./Kg./min.; see Fig. 1. 565 ml. were drawn, or 5.0% of the body weight.

TABLE IV

Exsanguination †*

Adult Male, 7.0 Kg.

Minutes	Pulmonary ventilation, L./15 sec.	Ventilation ratio	Respiratory rate, /15 sec.	Arterial O_2, vols. %	Arterial O_2 saturation, %	Arterial CO_2, vols. %	Arterial pCO_2, mm. Hg	$BHCO_3$, mM./L.	Lactic acid, mgm. %	pH	Hemoglobin, gm. %	Plasma proteins, gm. %	Pulse rate, per minute	Arterial blood pressure, mm. Hg: Systolic	Arterial blood pressure, mm. Hg: Diastolic	Pulse pressure, mm. Hg	Effective venous pressure, cm. H_2O	Intrathoracic pressure, cm. H_2O
0	4.20	15.4	50	23.3	100	35.8	25	18	0	7.49	15.2	7.6	118	178	86	92	16	4
8	8.00	30.0	56	20.9	100	31.8	23	16	0	7.46	14.7	7.6	168	166	96	70	14	—1
11	2.80	10.3	33			32.4	24	16	0	7.45	15.2	7.1	130	142	90	52	7	—3
14	3.40	12.5	20							7.39	15.3	6.8	125	123	75	48	—8	—12
18	2.30	8.5	24	23.2	100	27.1	26	13	20	7.33			104	76	34	42	—7	—2
22	1.67	6.1	20							7.35	15.5	7.1	79	58	30	28	—18	—16
26	1.05	3.9	11	23.7	100	27.7	33	13	70	7.21	15.0	7.2	110	64	34	30	—7	—4
30	.20	.7	5										30	36	9	27	—7	—6
34	.23	.9	5										32	32	9	23	—15	—6
36	0												50	16	4	12	—14	—8
38	0												40	7	0	7	—10	—3

*Dog was panting until the 23d minute.

†Blood was drawn at a rate of 2.0 ml./Kg./min.; see Fig. 1. 376 ml. were drawn, or 5.4% of the body weight.

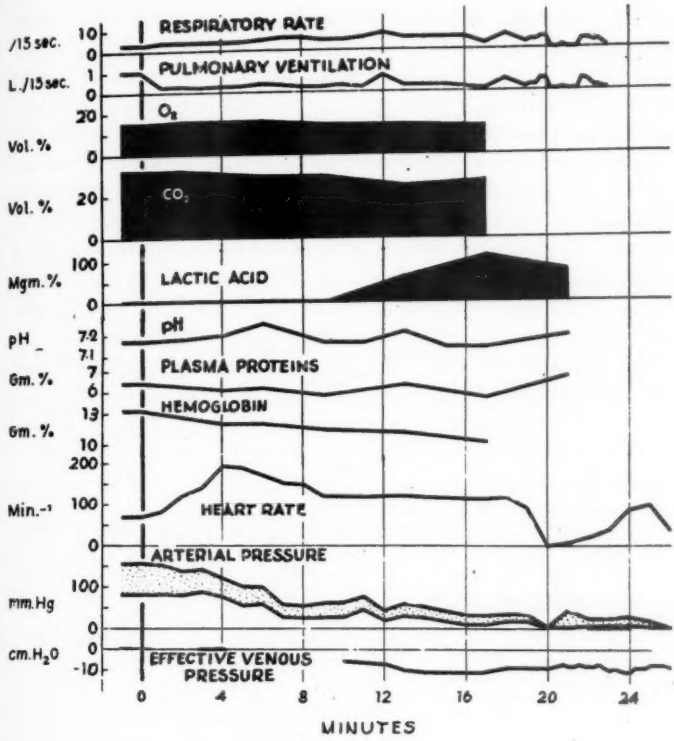

FIGURE 2

Course of death from exsanguination. Dog No. II.

The striking event in this experiment was the continuation of breathing for long periods after the blood pressure had fallen to very low levels and even after it was almost impossible to withdraw any arterial blood with a syringe. Thus, the four dogs continued to breathe for 18, 8, 25, and 6 min., respectively, after their arterial blood pressure had fallen below 50/25. (Figure 3 shows the records of dog III at 46 min.; the regular breathing at a blood pressure of 8/2 is illustrated.) Meanwhile, it became very difficult to obtain arterial blood samples; only by continued pulling on the

syringe plunger for one or two min. could an 8–12 ml. sample be obtained. In general, the time at which the last analysis of a blood sample is shown in the tables is the time at which it became impossible to draw samples worth analysis. Yet the dogs continued to breathe for many minutes thereafter and only stopped when the blood pressure had fallen to roughly 15/5. We continued to attempt to draw blood until the breathing ceased. For example, in dog IV the sample at 26 min. was drawn quickly but beyond this point, it took 1 or 2 min. to draw even 5 ml.; during the next 10 min., only 27 ml. could be withdrawn by persistent effort. Yet throughout 8 of these 10 min. the dog continued breathing. The tables all indicate the time at which breathing ceased and also indicate the decline in blood pressure beyond apnea.

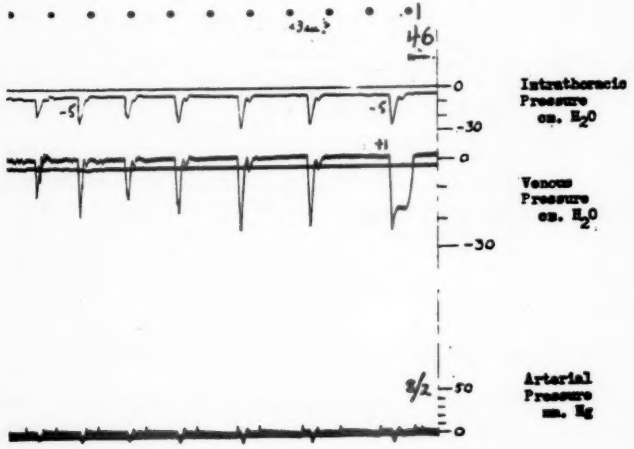

FIGURE 3

Arterial, venous and intrathoracic pressures at end of exsanguination. Dog No. III at 46 minutes.

The breathing was stimulated at about 15–20 min. after the start. (Dog IV was panting throughout most of the experiment and so is not included in this discussion of breathing.) This hypernea, to about 3 times the resting ventilation,

resulted in a decline in arterial CO_2-content and CO_2-tension. In spite of a late lactacidemia, the pH did not fall as severely as in the previous experiments. When the breathing stopped, it stopped relatively suddenly just as in the other experiments. No period of gasping and no dyspneic isolated gasps occurred in any of the dogs. Rather, the breathing became quiet, sometimes Cheyne-Stokes in type, and then abruptly ceased.

The arterial blood O_2-content remained high, at approximately full saturation, in all samples drawn. Because the dogs continued breathing usually until heart failure (see below), we feel confident that if samples could have been drawn late in the experiment, the O_2-content would have been found normal until apnea. About two-thirds of the way through the experiment, the dogs became insensitive to pain (pinch with hemostat) when the blood pressure was about 50/25, even though at these times the O_2-saturation of arterial blood was 100 per cent. Pulse rates were uniformly high during the experiment, except that terminally there occurred periods of great slowing or even transient arrest (see dog III). Pulse pressures uniformly declined throughout the experiment. In all experiments the effective venous pressure soon became negative, remaining low until death.

The question can be asked: what killed these dogs? Presumably, of course, they were killed by insufficient flow of oxygenated blood through vital tissues like the myocardium and respiratory center. It is because of this consideration that we have called this an "anoxic death." However, in this experiment, we did not demonstrate this; we were not able to show any reduced oxygenation of the arterial blood and we did not measure any rates of flow. Arterial pressures of the order of magnitude of roughly 25/10 are apparently adequate to maintain some flow, because at such pressures the dogs continued breathing and the heart continued contracting for a matter of minutes.

The hemoglobin content decreased in 3 of the 4 dogs to three-quarters of its starting value. This is the familiar mobilization of body fluids in hemorrhage shock (Harkins, 1941; Wiggers, 1942). That the mobilized fluid was primarily plasma

is shown by the fact that the plasma proteins did not change consistently, with one exception, throughout the experiment.

The P waves of the electrocardiogram continued to be essentially normal until circulatory failure. Occasional inversions, blocks or disappearances of short duration were noted. The ventricular complexes uniformly showed a gradually lowering voltage. At the time of lowered blood pressure, the QRS and the T waves were simple monophasic waves in opposite phase, with a short, almost isoelectric, ST segment. As mentioned above, there appeared terminally periods of strong bradycardia; whenever these occurred, the P waves disappeared.

Ventricular fibrillation occurred in 3 of the 4 dogs tested: at 43½ min. in No. I, just after heart failure; at 47 min. in No. III, just after heart failure; and at 41 min. in No. IV, 8 min. after heart failure. In dog No. IV, after 1 min. of fibrillation, the waves became isolated single monophasic waves which disappeared shortly after 45 min. In the dog whose heart did not fibrillate (No. II), the last complexes occurred at about 30 min.

Table V summarizes the terminal cardiac and respiratory pattern in hemorrhage. It shows that the last breath—it would be better to say "last breathing" because the final breaths were not of the gasping type—occurred at exceedingly low blood pressures, and that it was followed in a few seconds in 2 of the 4 dogs by cardiac arrest and then ventricular fibrillation. In the remaining two dogs (Nos. II and IV), both of which

TABLE V

Terminal Events in Exsanguination

No.	Rate of bleeding, ml./ Kg. min.	Last breath		Time of last discernible arterial pulsation	ECG	
		Time	Blood pressure		Time	Pattern
I	1.6	43:00	8/6	43:10	43:32	Ventricular fibrillation
II	2.0	23:21	30/9	26:15	30:00	Last complex (no fibrillation)
III	1.2	46:30	5/2	47:05	47:05	Ventricular fibrillation
IV	2.0	34:50	22/8	40:57	41:15	Ventricular fibrillation
					42:00	Single monophasic waves

were bled more rapidly and died sooner, breathing stopped at higher blood pressures, arterial pulsations continued for 3–6 min. after apnea and transient fibrillation took place in only one of the pair. These contrasting facts suggest that very severe hemorrhage may cause a different pattern in the terminal cardiorespiratory behavior from that of the less severe hemorrhages.

The second heart sound usually disappeared shortly before the first heart sound. The first sound disappeared when the blood pressure reached 22–30 mm. Hg systolic and 7–13 mm. Hg diastolic.

Discussion

In general, we confirm, using unanesthetized dogs, the reports of changes in heart rate, acid-base balance, mobilization of body fluids, and venous pressure that others report for hemorrhagic shock. There are however, many sharp differences between our experiments and others, with respect to the effects of hemorrhage upon the breathing and heart behavior just before death. While discussing these differences, it must be borne in mind that our experiment differs from others in two main aspects; first, our dogs were not under general anesthesia as were the other experiments; and second, the rate of hemorrhage differs in many experiments; *e.g.*, in Negovski's experiments (1945–1946), free bleeding from the femoral artery was allowed whereas in the experiments of Johnson and Blalock (1931) the animals were bled over periods of hours. We shall point out which of these factors appears critical in the explanation of the differences in results, but obviously the final word must await further explanation.

Wiggers (1923) described the terminal events in a fatal hemorrhage thus: "In the last analysis, death, of course, is due to the extreme reduction of cellular oxygen which results when arterial pressures are very low. Of all functions, however, respiration is the first to fail. The deep breathing progressively decreases and slow, shallow breathing supervenes. Finally, complete apnea, broken only by an occasional deep gasp occurs. This is usually accompanied by a further decline

in blood pressure, for the 'pressor effect' of respiration is entirely removed. Soon the heart beats become slow, but of great amplitude and vigor, thus making a last and final attempt to elevate the pressure and restore an adequate blood supply to the medulla. This may be successful for a time, but finally fails for want of oxygen." Negovski (1945–1946) reports, by and large, a similar train of events.

In our first experiment, the first function to fail is that of the brain, the dogs becoming unconscious (pain reflexes absent) about two-thirds of the way through the experiment. Furthermore, in no case did the dogs have a pronounced respiratory stimulation of gasping breathing or slow but strong heart beats. Rather, the respiration continued evenly, with only mild stimulation, until it suddenly ceased at the exceedingly low blood pressure of about 15/5, with the heart rate sometimes slowing, but the pulse pressure never rising greatly. These differences, it appears to us likely, are due primarily to the general anesthesia usually employed in studying hemorrhage. As is widely recognized (see Swann and Brucer, 1949a), the anesthetized dog's breathing is depressed. Presumably, it does not respond to the stimulus of hemorrhage adequately, and hence considerable arterial anoxia supervenes, as shown by Aub and Cunningham (1920), Doi (1921), and Negovski (1945–1946). This would lead to breathing of the gasping type and then to apnea, an effect readily seen in dogs breathing nitrogen (Swann and Brucer, 1949a). After the onset of apnea, heart failure would rapidly supervene. However, if the dogs' arterial blood was *not* anoxic and thus they continued breathing, as happened in our experience, life would be preserved for a long time. Indeed, in our experience, the event that killed the dogs in 2 out of 4 cases was ventricular fibrillation rather than progressive anoxia from apnea (see below). Negovski (1945–1946) defines "clinical death" as commencing just after the last gasp. But we think it likely that if he had not used anesthetics in his experiments, the onset of apnea and hence of "clinical death" would have supervened much longer after the start of hemorrhage than he reports.

It is widely recognized that in shock, man and animals are profoundly sensitive to anesthetics and opiates (Wiggers,

Eberly, and Wenner, 1912; Cannon, 1919, 1923; Harkins, 1941). The explanation is thought to lie in the respiratory depression which general anesthetics and opiates cause. Our dogs, for example, continued breathing far longer than anesthetized dogs subjected to a similar rate of bleeding. In the experiments of Lehman and Amole (1938) where amytal was used, the rate of bleeding was about the same as ours. But their dogs died on the average, after 32 ml. of blood per Kg. had been withdrawn, whereas, our unanesthetized dogs died only after 50 ml. of blood per Kg. had on the average been drawn.

Negovski (1945) states (p. 441) that the last "heart action" occurs at about 6 min. before the last breath. This we did not confirm, for as Table V shows, pulsations in the artery continued in two of the dogs for 3 or 5 min. beyond the last breath and in the other two dogs, the last breath, the last ventricular contraction and ventricular fibrillation were more or less simultaneous. By and large, however, these differences are more apparent than real: in Negovski's experiments, a mercury manometer was used to record blood pressure and with this instrument he would not have been able to detect the exceedingly weak cardiac contractions that continued in our experience to occur for such long periods.

Ventricular fibrillation has usually been considered an irremediable accident for all practical purposes (Wegria, 1944), but recently in many instances a fibrillating heart has been restored to normal rhythm with drugs, massage, countershock, etc. (Beck, 1941; Dripps, Kirbey, Johnson, and Erb, 1948; Lampson, Schaeffer and Lincoln, 1948; Touroff and Adelman, 1949). This has occurred in surgical practice, but one could not expect such treatment for men dying of accidental hemorrhage. From this aspect, the old dictum that ventricular fibrillation is, for all practical purposes, irreversible appears to hold good. However, from our study another qualification must be added: in the series of 37 dogs studied in 9 types of anoxic death, in 4 dogs ventricular fibrillation has appeared, as shown on the ECG, but then rhythmic electrical discharges have spontaneously reappeared: viz. dog IV in fulminating anoxia (Swann and Brucer, 1949a), dog IV in acute anoxia (Swann

and Brucer, 1949b), dog I in fresh water drowning (Swann and Brucer, 1949f), and dog IV in exsanguination. Hence we conclude that ventricular fibrillation may sometimes spontaneously revert to regular rhythm, and consequently that its appearance in anoxia is not an infallible sign of death. But there is no question but that its appearance is exceedingly dangerous to the organism and that usually it is a disastrous and irreversible accident. We think it probable that many of Negovski's (1945–1946) failures to resuscitate after exsanguination may be ascribed to the accident.

Ventricular fibrillation, including the data from all types of anoxia studied in this series, has taken place 12 times in 37 dogs. Of these 12, 4 were temporary fibrillations as discussed above, and 8 were permanent, *i.e.*, they did not spontaneously revert to normal rhythms. Also, out of the total of 12 fibrillations, 4 took place in fresh water drowning and 3 in exsanguination. In a larger series of dogs studied in the anoxia consequent to breathing N_2 or 2.43 per cent O_2 or 1 per cent CO, the accident seldom occurs (Swann, 1949). Hence we conclude that ventricular fibrillation occurs only very seldom in simple anoxic death in dogs; in fresh water drowning or exsanguination it appears commonly, but in other types of anoxic death it is rare.

Resnik (1925) and Wegria (1944) both consider that ventricular fibrillation is prone to develop in anoxia. We dissent from this conclusion: our data furnish clear evidence that, with the exceptions of fresh water drowning and exsanguination, the accident occurs only rarely. We feel confident that our conclusion may be applied unreservedly to dogs. In attempting to appraise the situation in man, it must be borne in mind that there is considerable species difference in the reaction. In small animals (cats, rabbits, rats), it is recognized that although ventricular fibrillation may occur, it frequently reverts to regular conduction rhythm (Wegria, 1944; Ogden, 1949). It seems possible that the larger the heart involved, the more likely would such a heart remain permanently in a state of ventricular fibrillation. If true, the prognosis for ventricular fibrillation in man with his large heart is poor. Although the condition sometimes appears transiently in men

(see Schwartz, Leiner, and Michtom, 1949), this would appear to be a different phenomenon from a ventricular fibrillation precipitated by anoxia, cardiac manipulation or anesthesia.

In summary, therefore, arguing primarily from the behavior of infrahuman species, we suspect that in man ventricular fibrillation is rare in the following types of overwhelming fatal accident: the anoxia of breathing gas mixtures low in oxygen content or tension, carbon monoxide poisoning, obstructive asphyxia, and sea water drowning. In fresh water drowning and severe hemorrhage, the accident appears to be common. Once the process has started, furthermore, from whatever cause, unless the victim is actually undergoing surgery and so can be treated promptly with cardiac massage, etc., ventricular fibrillation will probably not revert to normal conduction rhythm except in rare instances.

The tachycardia and low pulse pressure—the "weak thready pulse" which are so characteristic of shock—occurred prominently in all experiments. In our experience, the femoral pulse becomes impalpable in the dog when the blood pressure falls below about 56/35 (Swann, 1949). Since our dogs lived 5–20 min. with blood pressures below 56/35, it is apparent that the presence or absence of a palpable pulse cannot be used as criterion of death.

The effect venous pressure was found at circulatory failure to be from 6 to 14 cm. H_2O subatmospheric. In 2 of the 4 dogs (Nos. II and IV), it had decreased to the level found at death at about half way through the exsanguination. We did not observe consistently the sharp decline in effective venous pressure that Wiggers (1918) reported in traumatic shock.

The low effective venous pressure at death which occurred in these dogs is taken as a sign of "forward failure of the peripheral circulation" (Harrison, 1938). And yet because of the inconsistency of the change, we are very dissatisfied with the measurement even in hemorrhage. In all of these dogs the blood volume was certainly greatly reduced by the hemorrhage and we would certainly expect the effective venous pressure to be consistently low. In 2 of the 4 dogs the pressure fell, as circulatory failure approached, to about — 10 cm. H_2O (Nos. II and IV), but in the other two it fell only to — 2 cm.

Even in hemorrhage, therefore, measurements of the effective venous pressure give such inconsistent results that they cannot be used to appraise the state of the circulation.

Determining the effect of the hyperlactacidemia on the blood bicarbonate, as done previously (Swann and Brucer, 1949b), each mE. of lactic acid was found to preempt 0.5 mE. of $BHCO_3$. The changes in acid-base equilibrium followed in general the pathway of metabolic acidosis described by Cannon (1923). In his, and others', experiments, the decline in alkali reserve and in blood bicarbonate started when the (diastolic) blood pressure fell below 80 mm. Hg. But in our experience, the decline started when the diastolic pressure fell to 30–40 mm. Hg, and simultaneously, as we have indicated, with the rise in blood lactate. The difference is presumably, again, a matter of the absence of general anesthesia in our experiment. Cannon (1923) and others were of the opinion that the flow of blood in hemorrhagic shock was so greatly slowed when the blood pressure fell below 80 mm. Hg that tissue oxidation became incomplete and that therefore lactic acid started to accumulate. This explanation is undoubtedly correct, providing that the level of blood pressure at which anemic anoxia causes acidosis, in the absence of general anesthesia, is set at about 80/40. Scanty blood flow, it must be noted, is probably *not* the cause of the hyperlactacidemias and metabolic acidoses of the other anoxias we have studied. Rather, we consider them a matter of defective oxidation from low arterial O_2-tensions and as well reflex action involving the sympathetic nervous system (Himwich, 1932).

Summary

Simultaneous measurements are reported of the breathing, systolic and diastolic blood pressures, effective venous pressure, electrocardiograms, heart sounds, blood gases, pH, lactic acid, hemoglobin and plasma proteins of dogs, under local anesthesia, during the anoxic death caused by exsanguination. The dogs were bled at a rate of 1.2–2.0 ml./Kg./min.

The breathing continued until the systemic blood pressure had fallen to about 15/5; it continued at a time when there were no audible heart sounds and no palpable pulse and when

the blood flow was so small that only with great difficulty could any arterial blood be withdrawn. In 2 of 4 dogs, the breathing finally stopped at blood pressures of about 6/4, to be followed in a few seconds by cardiac arrest and ventricular fibrillation. The relatively long survival of our dogs compared with those reported in others' studies is ascribed to the absence of general anesthesia during our experiments.

The rareness of ventricular fibrillation in overwhelming anoxic death is discussed, as is the appearance of transient ventribular fibrillation. It is suggested that in man the only types of overwhelming anoxic accident in which ventricular fibrillation occurs commonly are fresh water drowning and severe hemorrhage.

The onset of the metabolic acidosis of hemorrhage appears, in the absence of general anesthesia, at a blood pressure of about 80/40.

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THE LIMITATIONS OF HALOGENATED PYRIMIDINES AS RADIOLOGIC CONTRAST MEDIA

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The halogenated pyridine derivatives, iodopyracet U. S. P. (diodrast) and Na iodomethamate N. N. R. (neo-iopax), have long been used successfully as relatively non-toxic contrast media for urography. The various halogenated pyrimidines have not, to our knowledge, been studied as radiopaque diagnostic aids. The possibility that pyrimidine derivatives might have a selective organotropy for the pancreas or thyroid is suggested by biochemical evidence of the damaging effect of certain of them on the endocrine function of these organs (Astwood, 1943; Dunn et al., 1943), although cytologic study of other organs shows a general cytotoxic action of alloxan (Thomas and Emerson, 1945; Thomas et al., 1949). Alloxan diabetes also affects the exocrine function of the pancreas, in that the response to secretin is decreased (Grossman and Ivy, 1946), and a selective damage of intralobular duct cells is apparent microscopically. Since there are no suitable agents available for parenteral tests of pancreatic function or for radiologic visualization of this organ, certain halogenated pyrimidines previously shown to be nondiabetogenic (Emerson, Ewing and Thomas, 1947) were tested in rats and dogs for radiologic evidence of selective distribution.

The following agents were available in adequate quantities for X-ray studies of tissue distribution: 5-ioduracil, prepared by the method of Johnson and Johns (1905/06); an iodinated product of the same reaction with 6-methyluracil, presumably 5-iodo-6-methyluracil but possibly the corresponding β-ureidocrotonic acid derivative or the dimer, $C_{10}H_{12}O_5N_4I_2$, which had physical properties different from those of 5-iodouracil; 5-

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bromouracil, prepared according to Wheeler and Merriam (1903); 5-bromo-1,3-dimethyluracil, prepared by the method of Johnson and Clapp (1908); 5-bromo-6-methylhydrouracil, prepared according to Fischer and Roeder (1901); 5-bromo-6-hydroxyhydrothymine, prepared by the method of Baudisch and Davidson (1925); 5,5-dibromo-6-hydroxyhydrouracil, first prepared by Johnson (1908); 5,5-dibromobarbituric acid (dibromin N. N. R. 1941), recrystallized from an Eastman Kodak Company product; and 2-amino-4-hydroxy-5-bromopyrimidine, generously supplied to us by the Stamford Research Laboratories of the American Cyanamid Company. All these agents but dibromin had been tested by intramuscular injection in mice for diabetogenic effect and for antagonism towards alloxan simultaneously administered, and were found to have neither effect. They were all tolerated in mice in intramuscular doses of 0.5 mM/kg., and only 5,5-dibromo-6-hydroxyhydrouracil was lethal at 1.0 mM/kg.

The halogen content of the agents tested is sufficiently high to ensure good X-ray contrast, and approximates, for iodouracil, 53%; iodomethyluracil, 50%; bromouracil, 42%; bromodimethyluracil, 36.5%; dibromohydroxyhydrouracil, 55.5%; bromomethylhydrouracil, 39%; bromohydroxyhydrothymine, 36%; aminohydroxybromopyrimidine, 42%; and dibromin, 56%. However, the solubility of all the agents except dibromohydroxyhydrouracil, bromohydroxyhydrothymine and dibromin is well below 25 mM/1. in water or saline at room temperature, or, roughly, $<0.5\%$. In contrast, iodopyracet concentrated solution N. N. R. contains 70% of the agent, and Na iodomethamate is available in 50 and 75% solutions.

Figure 1 illustrates the radiologic picture 3 hours after 2 g/kg. (approx. 8 mM/kg.) of iodouracil were given intragastrically to a dog weighing 3.9 kg. Previously exposures showed the agent in the stomach, and later the passage of the radiopaque material through the gastrointestinal tract. Findings were similar in a dog given 0.3 g/kg. of bromodimethyluracil, in which case a marked toxic depression of the dog occurred.

FIGURE 1
Iodouracil in colon of dog after oral administration.

Figure 2 shows the radiologic appearance of a rat 2 hours after intragastric administration of 1 mM/kg. of iodouracil. Similar findings were apparent in rats treated with the same dose of the other 8 agents studied.

FIGURE 2

Iodouracil in rat after oral administration.

Figure 3 is of a dog 2 hours after treatment with iodouracil, after operative treatment to localize the pancreatic area and the gall bladder by means of a fine Pt wire loop about the former and a wound clip near the latter.

FIGURE 3

Iodouracil in dog after oral administration. Note absence of shadow in region of pancreas, outlined with Pt wire, and in gall bladder, near upper wound clip.

Figure 4 shows the appearance of rats 10 hours after treatment with 2 mM/kg. intragastric doses of the 9 agents. The rats were then killed, their pancreases removed, and the radiopacity of the pancreases was compared with that of normal spleens. With comparable thicknesses of tissue, there was no significant difference in opacity, indicating lack of selective pancreotropic properties of these agents.

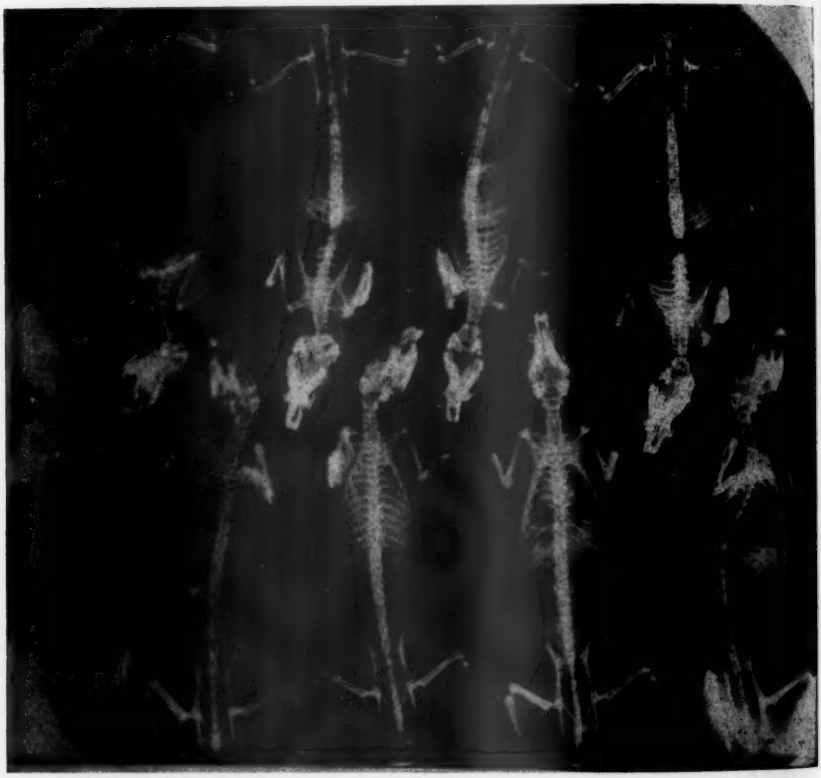

FIGURE 4

Absence of halogenated pyrimidines in rats 10 hours after oral administration of the 9 agents in the order (left to right, bottom row; left to right, top row) in which the agents are named in the text.

Summary

After oral administration of 9 iodinated or brominated pyrimidines, no selective concentration of any of the halogenated pyrimidines occurs in the pancreas, and in none of the rats or dogs so treated did the thyroid cast a shadow. The low solubility of these agents may limit their absorption; the bladder in none of the animals showed any contrast. Since parenteral injection of these agents is not feasible, they do not have any application as useful diagnostic aids in roentgenography.

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GASTROSCOPY—AN EVALUATION OF GASTROSCOPIC, ROENTGENOGRAPHIC AND PATHOLOGIC FINDINGS IN 60 CASES*

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The modern era of gastroscopy may be said to begin with the introduction of the flexible gastroscope by Schindler in 1932 (Schindler, 1937). Gastroscopy has established itself during the subsequent years, as a safe and useful diagnostic procedure; on the one hand, as a method supplemental to roentgenologic examination, and, on the other hand, as a specific method by which the gastric mucosa may be studied. As experience with the use of this instrument has been gained, recognition of its limitations and idiosyncrasies became manifest. The seeming contradiction that a method which can contribute "important and decisive information" (Jones, 1947) may instead add to the difficulties in establishing a correct diagnosis, "places it," according to Jones (1947), "in a position no different from that of all diagnostic measures."

There is agreement (Moersche, 1946; Jones, 1947) that gastroscopy is the superior method for the diagnosis of chronic gastritis and for the recognition of polyps. For other types of gastric disease, the method is of supplementary value only. Correct diagnosis is not always attained when gastroscopy is used in conjunction with X-ray examination of the stomach (Benedict, 1946; Renshaw et al.; 1942; Rickets et al., 1946). The claim has been made (Benedict, 1947) that the gastroscopist's chances of a correct diagnosis are greater than those of the roentgenologist, if the former can view the lesion adequately. It has been said (Templeton and Boyer, 1942) that in those instances where a lesion is diagnosed benign by one method and malignant by the other, "when the facts finally become known it will be found that the gastroscopist is no more or no less likely to be correct than is his colleague, the roentgenologist."

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Gastroscopy is not recommended for routine diagnosis of stomach disease (Johnson, 1946; Benedict, 1947). Its use should not be contemplated until a comprehensive clinical study of a patient has been completed. Then it should be reserved for (1) those borderline cases where there is a decision to be made as to the type of therapy, *i.e.*, medical or surgical; (2) those cases where the symptomatology is not adequately explained by other diagnostic procedures; (3) those cases of unexplained hemorrhage from the gastro-intestinal tract; and (4) for purposes of teaching and research.

The contra-indications for gastroscopy are, broadly defined, any pathologic process or condition which obstructs, renders difficult or dangerous the passage of the instrument into the stomach.

Several limiting factors reduce the usefulness and impede the attainment of accurate diagnosis with the gastroscope. First, surface structure alone is seen. Schiff (1943) warns that "in looking through a gastroscope the clinician should constantly bear in mind that he is viewing only part of the mucosal surface of the stomach, not its entire surface nor its deeper layers or surrounding structures." Second, the entire mucosal surface of the stomach is not visualized at a gastroscopic examination. There exist rather constant "blind areas," namely, (a) the lesser curvature region of the antrum, (b) the small area of mucosal surface at the tip of the instrument, (c) a variable area of the greater curvature region in the fornix, (d) a larger or smaller area of the posterior wall, and (e) the lesser curvature surface of the cardia. The pylorus and distal portions of the antrum are not seen completely in approximately ten per cent of all gastroscopic examinations. Third, there is a large personal factor. The accuracy of diagnosis depends upon the skill and experience of the operator. The picture of the stomach mucosa, as seen by the gastroscopist, is constantly changing from time to time in the same individual. Fourth, technical difficulties may prevent adequate visualization of the stomach, *e.g.*, mechanical failure of the instrument, inability of stomach to retain air, inability of patient to co-operate sufficiently to conduct the examination.

Method of Study

A statistical study of sixty patients admitted to The University of Texas Medical Branch Hospitals, whose case histories contain data on gastroscopic, roentgenologic and pathologic examinations for disease of the stomach, is presented. The diagnosis of the presence or absence of gastric disease as made by gastroscopist and by the roentgenologist, respectively, is classified as correct, indefinite or incorrect in respect to the proven pathologic findings for each respective patient. The advantages and limitations of gastroscopy as defined by this study are evaluated. A few selected case histories are presented.

Results

The frequency of cases according to the gastric lesion and accuracy of gastroscopic or roentgenologic diagnosis is presented in Table I. There are, in this series of sixty cases, twenty-three carcinomas of the stomach, nine benign gastric ulcers, six instances of chronic gastritis, four postoperative stomachs, four stomachs with pyloric obstruction, one gastric syphilis, and thirteen stomachs in which no gross pathology is found. This latter group includes two stomachs in which a diagnosis of chronic gastritis is made by the gastroscopist but in which histological study of the respective mucosa is not reported.

A correct diagnosis was made in thirty-one or fifty-two per cent of the sixty cases by gastroscopic study alone, an indefinite diagnosis in seven or twelve per cent, and an incorrect diagnosis in twenty-two or thirty-six per cent. The lesion was not visible to the gastroscopist in seven of the group with incorrect diagnosis. The roentgenologist, in the same sixty individuals made a correct diagnosis in thirteen or twenty-two per cent, and an incorrect diagnosis in twenty or thirty-three per cent. A combination of both methods increased the number of accurate diagnosis to sixty-seven per cent. In twenty cases or thirty-three per cent, neither the gastroscopist nor the roentgenologist made a correct diagnosis. The conclusion may be drawn that gastroscopy does not compete against roentgenology in the accurate diagnosis of gastric disease but that it supplements the later procedure. A higher percentage of accurate

TABLE I

Frequency of Cases by Lesion and Accuracy of Diagnosis

Disease	Total	Gastroscopy I	II	III	IV	X-Ray I	II	III	IV
1. Carcinoma	23	12	5	6	3	16	5	2	2
2. Benign gastric ulcer	9	2	0	7	2	1	4	4	0
3. Chronic gastritis	6	3	1	2	1	1	0	5	2
4. Syphilis	1	0	0	1	0	0	0	1	0
5. Post operative	4	3	1	0	1	4	0	0	0
6. Benign plyoric obstruction	4	4	0	0	0	2	2	0	2
7. No lesion found	13	7	0	6	0	3	2	8	0
Total	60	31	7	22	7	27	13	20	6
Per cent	100	52	12	36	12	45	22	33	10

Code:

I. Diagnoses correct
II. Diagnoses indefinite
III. Diagnoses wrong
IV. Lesion not visualized

Summary:	No.	%
Correct Diagnosis		
1. X-ray alone	27	45
2. Plus gastroscopy	40	67
Incorrect Diagnosis		
1. Both Methods	20	33

diagnosis was reached by the use of both methods in the diagnosis of diseases of the stomach.

The frequency of correct diagnosis in respect to the location of the lesion in the stomach is presented in Table II. The lesions present in fifty-six of the sixty patients are classified in this maner. Those individuals proven to have no gross lesion of the stomach are classified as errors in the category in which the supposed lesion was assumed to be present.

There were eleven patients with prepyloric lesions. Approximately one half were correctly diagnosed before surgery or autopsy. The gastroscopist made the following errors: (1) three patients proven benign gastric lesions were diagnosed malignant; (2) three proven malignant lesions of the stomach were diagnosed benign; (3) one lesion was not diagnosed definitely as to the presence or absence of malignancy; (4) one lesion in the prepyloric area was not visualized. In three patients, the gastroscopist made a correct diagnosis (two normal stomachs; one gastric carcinoma) . The roentgenologist, in these same eleven patients, diagnosed two malignant and one benign gastric lesion correctly, but called the following conditions malignant: ulcerative gastritis (one patient), benign ulcer (one patient) and normal stomach (three patients). Two proven gastric carcinomas were missed by the roentgenologist. The following case histories illustrate the difficulties of correct diagnosis in this region of the stomach.

Case #1, G-203, W.M., fifty-five years. This man entered the hospital with a diagnosis of an organic lesion in the pyloric region. There was a history of upper abdominal distress, pyrosis, nausea, vomiting and weight loss during the eight or nine months previous to admission. Generalized abdominal tenderness was present. Gastric analysis showed free acid. No lesions were found at first by the roentgenologist, but on a subsequent examination, a slight irregular deformity of the prepyloric regions was demonstrated. Gastroscopic examination was not successful because of antral spasm. A second gastroscopy, one week later, showed a normal pylorus. There was an infiltrating polypoid mass on the posterior wall of the antrum. A diagnosis of carcinoma was made. A subsequent roentgenographic study demonstrated a slight irregular deformity of the

TABLE II

Comparison—Accuracy of Diagnosis with Location of Lesion

(56 Cases)

	Pre-pyloric		Antrum		Body		Cardiac		Entire	
	No.	%	No.	%	No.	%	No.	%	No.	%
Both Accurate	1	9	6	30	3	23	0	0	7	68
Both Indefinite	0	0	1	5	1	7	0	0	0	0
Inaccurate or no value	6	55	4	20	5	39	2	67	1	16
Gastroscopy Superior	2	18	5	25	3	23	1	33	1	16
X-Ray Superior	2	18	4	20	1	7	0	0	9	0
Totals	11	100	20	100	13	100	3	100	6	100

prepylorus and lesser curvature of the stomach which was interpreted to be an early malignant growth. A subtotal resection was done. Microscopic examination of the resected specimen showed a chronic hypertrophic, ulcerative gastritis.

Cacce #2, G-187, W.M., fifty-four years. For six months previous to hospital admission there had been abdominal fullness and distention, persistent belching, constipation and weight loss. Slight tenderness was present in the epigastrium. The gastric juice contained free acid. A constant deformity on the prepyloric region with considerable gastric retention was found by the roentgenologist. Gastroscopic examination showed several polyps covered with smooth mucosa lying near the greater curvature on the posterior antral wall. The mucosa of the antrum and body of the stomach appeared normal. The pylorus was not seen. The gastroscopist made a diagnosis of multiple benign polyps in the antrum. He was unable to rule out malignancy. Operation was advised but refused by the patient. Roentgenologic study two months later showed an obstructing carcinoma of the pylorus. This was confirmed at operation and by the pathologist.

The above two cases demonstrates the difficulty in judging whether a given prepyloric lesion is benign or malignant from the appearance seen through the gastroscope. It also illustrates that unless the gastroscopist is able to see all of the lesion in question, his diagnosis is most likely to be in error. In our experience, the true character of prepyloric lesions is best determined in vitro and not from in vivo interpretations of shadows or outward appearances.

Greater accuracy in the diagnosis made by the gastroscopist is found when lesions are located in the antrum and body of the stomach (Table II). It is in these portions of the stomach that the gastroscopist is able, provided the lesion can be seen, to make a high percentage of correct diagnosis. Oftentime, shallow ulcerations, which are not demonstrated by the roentgenologist, are seen. In the high fundic regions and in the cardia, the gastroscope is of little or no value in the detection of disease.

Table III compares the accuracy of the roentgenologic and gastroscopic diagnosis with the proven gastric disease found

TABLE III

Frequency Accurate Diagnoses

	Gastroscope Superior		X-Ray Superior		Both Correct		Both Indefinite		Both Wrong	
	No.	%	No.	%	No.	%	No.	%	No.	%
1. Carcinoma	3	13	6	26	10	43	2	9	2	9
2. Benign gastric ulcer	2	22	1	11	0	0	0	0	6	67
3. Chronic gastritis	2	34	0	0	1	16	0	0	3	50
4. Syphilis	0	0	0	0	0	0	0	0	1	100
5. Post operative	0	0	1	25	3	75	0	0	0	0
6. Pyloric obstruction	2	50	0	0	2	50	0	0	0	0
7. No lesion found	4	31	0	0	3	23	0	0	6	46
Total	13	22	8	13	19	32	2	3	18	30

at surgery or autopsy. *Carcinoma of Stomach:* There are twenty-three patients with carcinoma of the stomach. A correct diagnosis is made by both methods in ten or forty-three per cent. The roentgenologist's diagnosis is correct and the gastroscopist's incorrect in six (twenty-six per cent) more patients. In three patients or thirteeen per cent, the diagnosis made at gastroscopy is correct. Of the six patients in which gastroscopy is proven to be of no value, the lesion could not be visualized by the gastroscopist in three instances. Neither method correctly evaluates the gastric pathology in four other patients. The presence or absence of malignancy could not be ruled out in two of these four patients. Both methods are in error in each of the remaining two patients. In the first of these latter patients, there is an infiltrating growth in the wall of the pyloric region which did not involve the mucosa. There is roentgenologic evidence of obstruction at the pylorus interpreted to be caused by a stenosing chronic duodenal ulcer. The gastroscopic examination showed a normal stomach with no intrinsic lesion present. The surgeon found an inoperable carcinoma of the pyloric region a few days later. In the second patient, the mucosal involvement of an infiltrating carcinoma is mistakenly diagnosed by the gastroscopist as a severe chronic superficial gastritis. This patient was gastroscoped seven times during a period of twelve months. At one time, the examiner thought that the process might be malignant, but apparent improvement observed a week later caused him to rule out this possibility. The roentgenologist found no lesion in this man's stomach on three successive studies made at intervals during the same year. A fourth examination, however, showed a large filling defect encroaching upon the lumen of the antrum and extending high into the body. There was an inoperable carcinoma of the stomach found at the time of exploratory laparotomy.

Much has been said about the early diagnosis of gastric carcinoma. Schindler (1947) writes that roentgenologic and gastroscopic techniques of stomach examination have attained such perfection that malignant lesions so small that the surgeon's palpating finger can not feel them have been detected by the combination of the two procedures. He urges that patients with the so-called precancerous conditions, namely, atrophic

gastritis, polyps and benign gastric ulcer (Schindler 1941) be routinely studied by X-ray and gastroscopy so that early malignant changes may be detected and treated promptly. Zinninger (1941) emphasizes the necessity of a well-trained observer being behind the gastrocope if the early diagnosis of cancer is to be made successfully. The gastroscope is useful in the early diagnosis of gastric cancer if the lesion involves the mucosa. In respect to the early diagnosis of an infiltrating lesion in which the mucosal is not involved until relatively late, the method leaves much to be desired. Repeated gastroscopic examinations do not always mean increasing accuracy. The danger of complacency in the presence of apparent benign mucosal changes always must be guarded against.

An analysis of twenty-one patients misdiagnosed carcinoma of the stomach by one or both methods is given in Table IV. The roentgenologist and the gastroscopist are in error in nine patients or forty-three per cent. Three of these patients had proven benign gastric ulcer, three had chronic gastritis, and the remaining three had no gross lesion. Carcinoma of the the stomach is suggested but not ruled out in five other patients. Finally, a correct diagnosis is made by the gastroscopist in

TABLE IV

Erroneous Diagnosis Carcinoma of Stomach

Anatomical Diagnosis	Total No.	Gastroscope I	II	III	X-Ray I	II	III
No lesion	9	4	0	5	0	2	7
Benign Gastric Ulcer	6	1	0	5	0	2	4
Chronic Gastritis	5	2	1	2	0	0	5
Syphilis	1	0	0	1	0	0	1
Total	21	7	1	13	0	4	17

Both methods wrong	9	43%
Both methods indefinite or one wrong	5	24%
Gastroscopy superior	7	33%
X-ray superior	0	0%
	21	100%

I. Diagnosis correct
II. Diagnosis indefinite
III. Diagnosis wrong

seven or thirty-three per cent of the group diagnosed as malignancy by the roentgenologist (six normal stomachs, one benign ulcer).

In summary, the routine diagnosis of gastric carcinoma is much more easily, quickly and satisfactorily done by the roentgenologist. The diagnosis will be correct in a majority of the cases. Gastroscopy should be reserved for those cases where there is doubt as to the character of the lesion, or the actual presence of a lesion, or where the X-ray findings do not explain adequately the clinical picture. The fact that the gastroscopist diagnosed the non-malignant character of seven lesions out of twenty-one misdiagnosed malignant by the roentgenologist is proof of the clinical value of gastroscopy.

Benign Gastric Ulcer: Only three patients with proven benign gastric ulcer were correctly diagnosed before surgery. The gastroscopist established the true character of the ulcer in two of these, while the roentgenologist made the correct diagnosis in the third. In this patient, the gastroscopist was unable to keep the stomach inflated and the lesion was not seen. A definite or a suggestively incorrect diagnosis of malignant ulcer was made by one or both methods in the remaining six patients. The history of one patient in the latter group was of interest. This negro man, age sixty-two years, told a typical peptic ulcer history. The roentgenologist was not certain that the ulcer crater observed on the lesser curvature in the middle third of the stomach represented a malignanant or benign lesion. The gastroscopist made a diagnosis of a benign ulcer at the first gastroscopy. During the following two months, two subsequent gastroscopic examinations showed no appreciable healing although some decrease in size of the ulcer niche was reported in subsequent roentgenological examinations. The gastroscopist felt that a definite diagnosis of benign ulcer could not be made and advised surgery. His suspicions of malignancy were not confirmed. The pathologist found a chronic benign peptic ulcer.

Schindler (1937, 1939, 1947) has maintained that the differentiation of benign and malignant gastric ulcer is much more easily and correctly attained by gastroscopic examination. According to Moersch and Kirklin (1946), Henning, Chevallier,

Freeman, Clerf and Wirts are of the same opinion, while Gutziet and Teitge and Rodgers are skeptical of such claims. Schiff (1943) emphasizes that the proof of benign or malignant character of a gastric ulcer rests on histological examination. Johnson (1946) states that the gastroscope may detect small ulcers missed by X-ray. He prefers resection to observation when the appearance of a lesion is indeterminate. He states that if the pathologist sometimes can not determine whether an ulcer is malignant or benign by looking at the gross specimen, it seems useless to expect the gastroscopist to do so.

The difficulties which beset the gastroscopist who attempts to diagnose the true character of gastric ulcer are further emphasized by the following case histories.

Case #3, G-188, W.M., eighty years. Symptoms consistent with peptic ulcer were present for eight years. On two previous occasions, he had been hospitalized for severe hematemesis. The diagnosis of peptic ulcer was never verified by roentgenologic examination. Gastroscopy on one of these occasions showed a patchy atrophic gastritis. A massive gastro-intestinal hemorrhage was responsible for his fourth hospital admission. A large ulcer crater, 2.0 cm. in diameter, was demonstrated on the lesser curvature of the body by the roentgenologist. Since there was a definite meniscus sign, the ulcer was believed to be malignant. Gastroscopic examination showed, in tangential view, a large ulcer crater located on the lesser curvature of the body. The edges were raised and rounded; the surrounding mucosa blended into them suggesting infiltration. The base was covered with a dirty gray exudate. The remainder of the stomach showed an extensive atrophic gastritis. The gastroscopist made a diagnosis of malignant gastric ulcer. A subtotal the ulcer were as described, but histologically, it was benign. resection of the stomach was done. The gross characteristics of The diagnosis of atrophic gastritis was confirmed by the pathologist.

The blending of the surrounding mucosa into the raised edges of this ulcer was strongly suggestive of malignancy. The presence of an extensive atrophic gastritis strengthened further this interpretation. The treatment pursued was correct

in view of the repeated severe hemorrhages from the stomach, even though the preoperative diagnosis was in error.

Case #4, G-234, N.F., thirty-nine years. This patient had a peptic ulcer of fourteen years duration. She was admitted to the hospital because of hematemesis and constant pain not relieved by therapy. Gastric juice contained free acid. The roentgenologist demonstrated changes suggestive of neoplastic ulceration in the prepyloric region and scarring of the duodenal bulb. Gastroscopy revealed a large punched out ulcer with rounded edges and a grayish base surrounded by normal mucosa located on the lesser curvature just proximal to the incisura. A diagnosis of benign ulcer was made. This was confirmed by the pathologist who found in addition to the ulcer described, another near the pylorus which was not seen at the time of gastroscopic examination. A hyperplastic catarrhal gastritis was found histologically although through the gastroscope the mucosa appeared normal.

The true character of this ulcer was recognized by the gastroscopist. Because of the inability to view the entire antrum, a second ulcer was not seen.

This inability to recognize the true character of gastric ulcer has been experienced by others. Benedict (1947) reports that in twenty-one cases of proven benign ulcer, only eight were diagnosed correctly by X-ray and gastrroscopy. Both methods were wrong in five cases, the gastroscopist was wrong in six more and the roentgenologist in another two. He summarized the reasons for this failure of gastroscopy as (1) the misinterpretation of apparent nodularity surrounding the ulcer, due to severe gastritis, as evidence of malignancy, (2) the inability to rule out malignancy when an unusual amount of rigidity surrounds the lesion, and (3) the desire of the gastroscopist and roentgenologist to err on the side of carcinoma.

Chronic Gastritis: There is little need to discuss the recognized superiority of the gastroscope in making a diagnosis of gastritis. It is pointed out, that the gastroscopist may not recognize gastritis which is apparent to the pathologist, or may misinterpret such changes as due to malignancy. This is particularly true of chronic ulcerative hypertrophic gastritis of the antral and prepyloric regions. Giant hypertrophic gasteritis

in the body of the stomach may produce X-ray appearances of malignancy (Maimon et al., 1947; Moersch, 1947; Montero et al., 1944). The following case history illustrates this problem.

Case #5, G-383, W.M., thirty-nine years. Ulcer-like symptoms which responded temporarily to symptomatic therapy had been present intermittently for five years. Free acid was present. A large, irregular filling defect extending from the fundus into the para media was interpreted by the roentgenologist as advanced carcinoma although an inflammatory condition could not be ruled out. Gastroscopy revealed a large mass of rugal folds resembling cerebral convolutions extending along the greater curvature of the body of the stomach. A diagnosis of giant hypertrophic gastritis was made although a malignant process was not definitely ruled out. The extensive deformity was not found at a second examination by the roentgenologist, but the rugae were said to be hypertrophied. A second gastroscopy showed findings similar to those present at the first examination. A definite diagnosis of hypertrophic gastritis was made. The patient was explored, the stomach opened and the large rugal folds were found as described by the gastroscopist. A biopsy specimen showed hypertrophic gastritis. The stomach was closed. Postoperatively the patient remained symptom free.

Normal Stomach: Some of the patients in this group were subjected to gastroscopic examination because a thorough investigation was desired in an obscure diagnostic problem. Others of the group were erroneously diagnosed as manifesting gastric pathology by either the gastroscopist or the roentgenologist. One patient in this group had bleeding from the gastro-intestinal tract of undetermined etiology which at autopsy was found to be due to varices of the esophagus. Of the thirteen patients, the correct diagnosis of a normal stomach was made in three by both procedures. The gastroscopic diagnosis was correct in four or thirty-one per cent while both methods were in error in six or forty-six per cent. At times gastroscopy will add some bit of indirect evidence which suggests the correct diagnosis of intra-abdominal extragastric pathology. A bulging of the posterior wall in the body of one otherwise gastroscopically normal stomach was interpreted as being due to an ex-

trinic mass, probably involving the body of the pancreas. A pancreatic tumor was suggested. Roentgenologic examinations of the entire gastro-intestinal tract were normal. The presence of an adenocarcinoma in the body of the pancreas was verified at surgical exploration. Moersch and Comfort (1939) report two patients with similar gastroscopic findings in whom the diagnosis of pancreatic tumor was suggested and verified.

Miscellaneous. The detection of marginal ulcer in the post-operative stomach may, at times, be made gastroscopically. X-ray examination of the obstructed stomach gives usually as much or more information than does gastroscopy except for the detection of chronic gastritis, where the latter method is superior. Gastroscopic examination may be of value in determining the cause of post-operative distress (Moersch and Walters, 1940). The case of gastric syphilis is of interest because of its rarity and because it demonstrates the difficulty in the differential diagnosis of infiltrative lesions by the gastroscope. In this particular case, the gastroscopist and roentgenologist both expressed the opinion that a carcinoma of the stomach was present. The pathologist established the correct diagnosis.

Summary and Conclusions

1. Sixty patients with proven gastric disease are analyzed as to the accuracy of diagnosis as made by the methods of roentgenology and gastroscopy. A correct diagnosis is reached by both procedures in nineteen or thirty-two per cent; and incorrect diagnosis in eighteen or thirty per cent; and an indefinite diagnosis in two or three per cent. Correct diagnosis, as a result of gastroscopy alone is made in thirteen or twenty-two per cent, while the X-ray examination gave the correct result in eight or thirteen per cent. By application of both methods to this group of sixty patients, a correct diagnosis of gastric disease is obtained in forty or sixty-seven per cent.

2. Gastroscopy is a valuable method of diagnosis for the clinician because it supplements roentgenologic procedures and often yields definite information in its own right. A higher degree of accuracy is obtained when roentgenology and gastroscopy are combined in the diagnosis of gastric disease. Neither

method, either by itself or in conjunction with the other, will assure an infallible diagnosis.

3. Failure to make an accurate diagnosis by gastroscopy is found due to (1) the inability of the gastroscopist to visualize a lesion deeper than its surface; (2) the impossibility of viewing adequately all regions of the stomach; (3) the misinterpretation of the changes observed; and (4) technical failure.

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AN APPARATUS FOR STUDYING ELECTROCARDIOGRAPHIC CHANGES IN SMALL ANIMALS*

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The electrocardiographic manifestations in normal and abnormal conditions of man and larger animals have been the subject for many investigations. However, similar studies in smaller animals, such as rats, mice, and guinea pigs, have been hindered because of the lack of adequate equipment.

Rappaport and Rappaport (1943) apparently were the first to point out that galvanometric speeds, such as are employed in commercially available electrocardiographs, introduce error in small animal applications. To overcome this difficulty, they employed a vacuum tube amplifier with an Einthoven string galvanometer and obtained string speeds up to 0.0015 second.

Hundley, Ashburn, and Sebrell (1945), using an apparatus similar to that described by Rappaport and Rappaport, obtained good electrocardiographic tracings on experimental rats. Others have made studies on small animals without the use of an amplifier, but such studies apparently do not represent true electrocardiograms.

Cardiac damage in Chagas' disease is an established fact, Chagas (1909). Certain electrocardiographic changes in man and larger animals, presumably due to Chagas' disease, have been recorded by Chagas (1930). Although myocardial lesions have been shown to occur in mice and guinea pigs as early as 21 to 23 days after inoculation with *Trypanosoma cruzi*, Packchanian (1939 and 1940), no adequate electrocardiographic studies have been made on these animals up to the present time.

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In our endeavor to study electrocardiographic changes in small animals experimentally infected with Chagas' disease, it was found necessary, before proceeding with such studies, to develop and standardize the technique for obtaining good electrocardiographic tracings in small animals.

The object of the present communication is to describe an apparatus which, in the hands of the writers, has been found satisfactory in the reproduction of true electrocardiograms in small animals such as guinea pigs and mice.

Description and the Use of Apparatus

The apparatus used consists of four basic units: (a) an Einthoven string galvanometer with camera, (b) a boosting amplifier, (c) a coupling unit, (d) patient cable leads, and (e) a ground wire (see Figure 1).

The string galvanometer was modified to increase the camera speed from 25 millimeters per second to 50 and 75 millimeters per second by the use of suitable pulleys, and the string tension was increased from 1 centimeter per millivolt to 0.5 centimeter per 3 millivolts sensitivity.

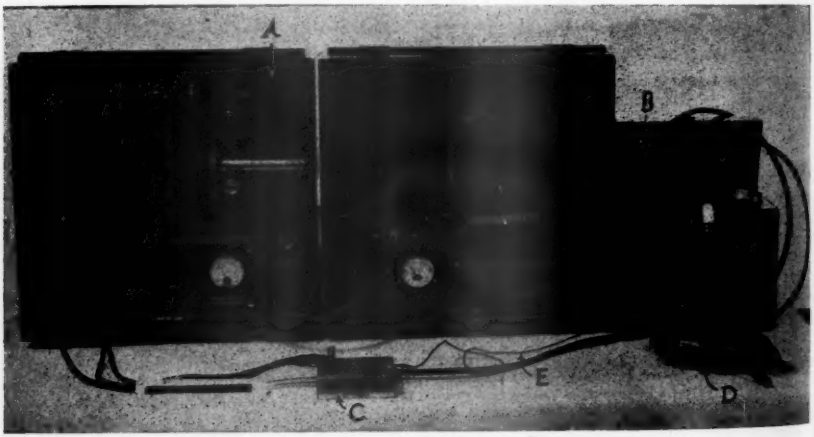

Figure 1

Electrocardiographic assembly (A) string electrocardiograph, (B) amplifier, (C) coupling unit, (D) patient cable leads, (E) ground wire.

The booster amplifier consists of a standard three limb patient cable connected to a lead selector switch, followed by a three stage resistance capacity coupled amplifier (see Figure 1-b).

The coupling unit, shown schematically (see Figure 2) is used between the string galvanometer and the booster amplifier. This unit consists primarily of an attenuator to drop the booster output to a suitable level for use with the string galvanometer, and in addition, it contains a shunt condenser which flattens the frequency response curve of the system, which otherwise would have a hump due to insufficient damping of the tight string, Miller (1948).

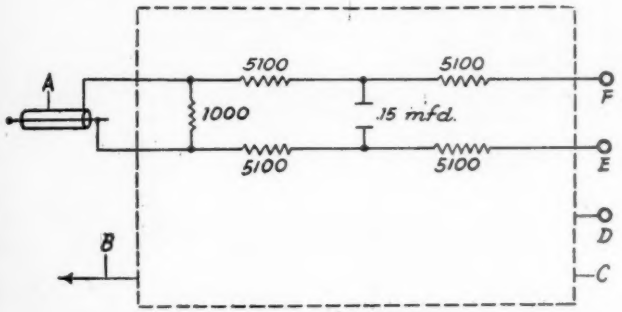

Figure 2. Sketch showing coupling unit: (A) phone plug to amplifier output; (B) ground wire to amplifier panel; (C) metal case; (D), (E), (F), left leg lead, left arm lead, and right arm lead respectively, from binding posts of coupling unit to string electrocardiograph.

The electrodes used are copper plates 1 x 1.5 centimeters with binding posts to connect to the patient leads (see Figures 3 and 4).

The electrocardiographic tracings obtained in guinea pigs were performed without anesthesia, by securing the animal in the supine position on a suitable board (see Figure 3). The hair on the legs of the animal was clipped and standard electrode jelly was briskly rubbed into the skin. An electrode was

then placed on each foreleg and the left rear leg, and held firmly in place with rubber straps. Special efforts were made to avoid any mechanical injury to the animal.

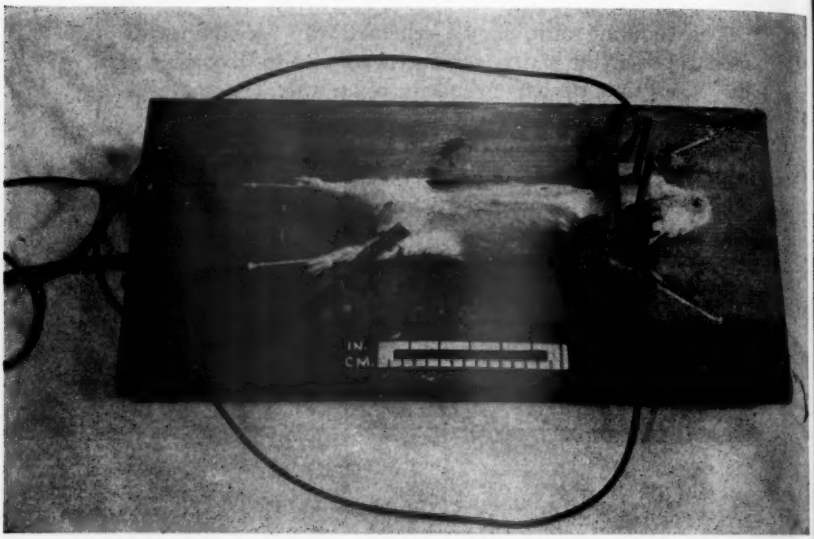

FIGURE 3

Guinea pig in supine position on animal board with electrodes and patient cables attached: (A) L.L.; (B) L.A.; (C) R.A.

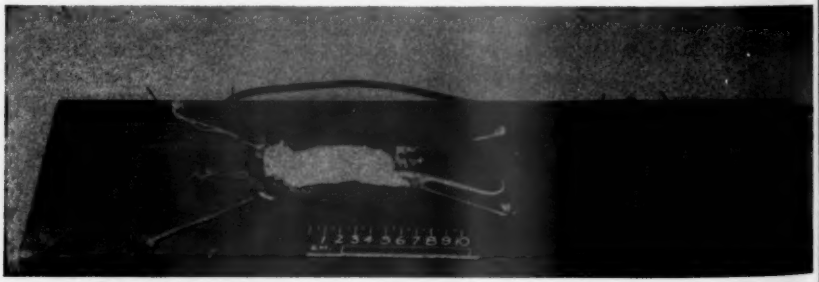

FIGURE 4

Mouse in supine position on animal board with electrodes and patient cables attached.

The electrocardiograms in mice were recorded in essentially the same manner as described for guinea pigs, with the exception that the animal board was somewhat smaller (see Figure 4).

Care was taken to eliminate as much as possible interfering alternating current by grounding the galvanometer and amplifier, and by using a line filter between galvanometer and power line. In an effort to still further reduce interfer-

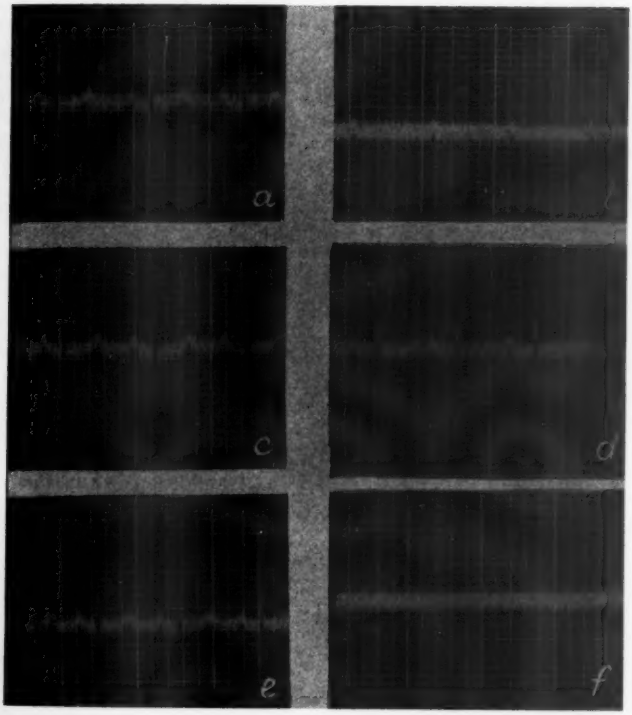

FIGURE 5

Typical Electrocardiogram of Normal Guinea Pig. (a) Lead I with amplifier, (b) Lead I without amplifier, (c) Lead II with amplifier, (d) Lead II without amplifier, (e) Lead III with amplifier, (f) Lead III without amplifier. (Taken at Camera Speed 50 mm. per second.)

ing radiation, the animal board and amplifier unit were placed in a grounded copper-screened cage.

Electrocardiographic Observations in Normal Guinea Pigs

Using the equipment described above, satisfactory electrocardiograms on normal guinea pigs were obtained (see Figures 5 and 6). In spite of the rapid heart rate, the various

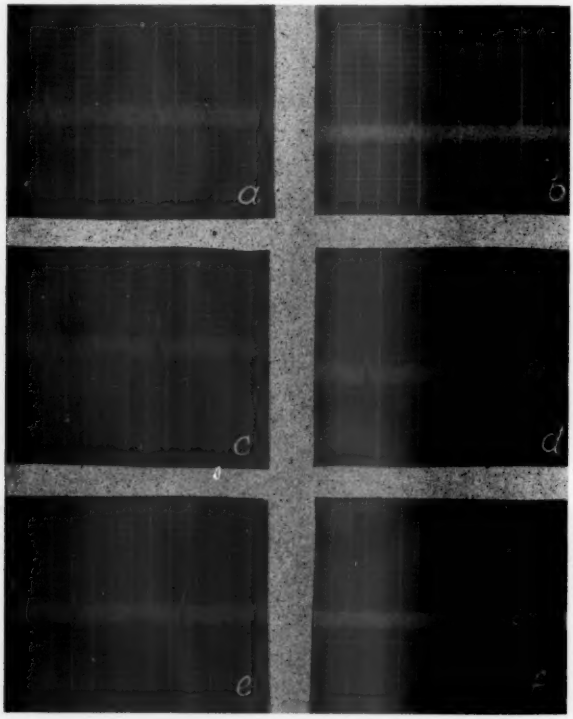

Figure 6

Typical Electrocardiogram of Normal Guinea Pig. (a) Lead I with amplifier, (b) Lead I without amplifier, (c) Lead II with amplifier, (d) Lead II without amplifier, (e) Lead III with amplifier, (f) Lead III without amplifier. (Taken at Camera Speed 75 mm. per second.)

complexes were distinct and significant. Forty-five male guinea pigs were used as a basis for determining the normal electrocardiogram of the guinea pig. See Table I. A negative T was found in one guinea pig. ST takeoffs were at the isoelectric line in all electrocardiograms.

TABLE I

Electrocardiographic Data for 45 Normal Guinea Pigs

Observations	Mean	Range
Heart Rate	301 ± 12 per minute	240 to 360
P-R Interval (conduction time)	0.072 ± 0.003 seconds	0.06 to 0.09
Height of R_2 Waves	0.665 ± 0.096 millivolts	0.3 to 1.4
Height of T_2 Waves	0.062 ± 0.013 millivolts	0.00 to 0.15

ELECTROCARDIOGRAPHIC OBSERVATIONS IN NORMAL MICE *(Mus musculus)*

Despite rapid heart rates in mice, electrocardiographic tracings with the use of the amplifier were clear and readable (see Figures 7 and 8). Twenty male and twenty female adult mice *(Mus musculus)* were used in these observations. See Table II. Five of the mice in this group showed marked bradycardias and were therefore dropped from the series.

TABLE II

Electrocardiographic Data for 40 Normal Mice (Mus musculus)

Observations	Mean	Range
Heart Rate	635.7 ± 8.5 per minute	560 to 720
P-R Interval (conduction time)	0.038 ± 0.00077 seconds	0.03 to 0.05
Height of R_2 Waves	0.714 ± 0.045 millivolts	0.4 to 1.3
Height of T_2 Waves	0.254 ± 0.011 millivolts	0.15 to 0.37

Electrocardiograms were taken also on mice and guinea pigs without the booster amplifier on the galvanometer described in this article. This did not permit critical study of the mouse electrocardiogram, in spite of the fact the maximum sensitivity was used (see Figures 5 to 8).

SUMMARY

1. An electrocardiographic apparatus is described which facilitates accurate electrocardiographic studies in small experimental animals such as guinea pigs and mice.

2. An Einthoven string electrocardiograph with camera speeds of 50 and 75 mm. per second, and a string speed of 0.0015 seconds connected to booster amplifier by coupling unit was found to be satisfactory for the animals tested.

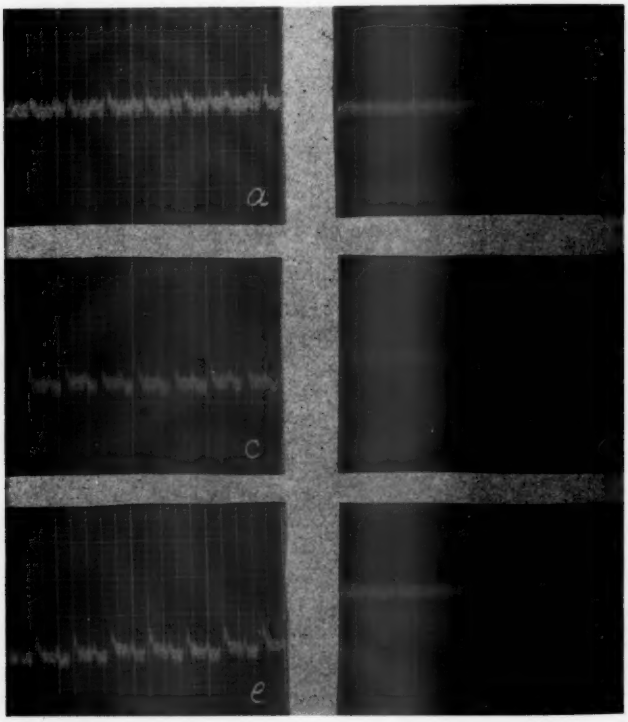

FIGURE 7

Typical Electrocardiogram of Normal Mouse *(Mus musculus)*. (a) Lead I with amplifier, (b) Lead I without amplifier, (c) Lead II with amplifier, (d) Lead II without amplifier, (e) Lead III with amplifier, (f) Lead III without amplifier. (Taken at Camera Speed 50 mm. per second.)

3. Of 45 guinea pigs tested, satisfactory electrocardiographic tracings were obtained. The findings consisted of heart rates ranging from 240 to 360 per minute with a mean of 301 ± 12 per minute, P-R intervals from 0.06 to 0.09 seconds with a mean of 0.072 ± 0.003 seconds, R_2 waves with a height from 0.3 to 1.4 millivolts and a mean of 0.665 ± 0.096 millivolts, and T_2 waves from 0.00 to 0.15 millivolts with a mean of 0.062 ± 0.13 millivolts.

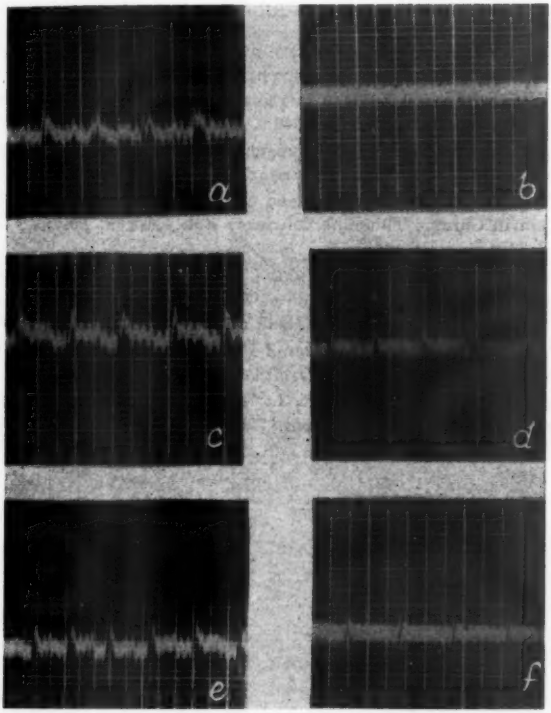

FIGURE 8

Typical Electrocardiogram of Normal Mouse *(Mus musculus)*. (a) Lead I with amplifier, (b) Lead I without amplifier, (c) Lead II with amplifier, (d) Lead II without amplifier, (e) Lead III with amplifier, (f) Lead III without amplifier. (Taken at Camera Speed 75 mm. per second.)

4. Forty mice *(Mus musculus)* were tested and all electrocardiographic tracings were easily readable. The heart rates ranged from 560 to 720 per minute with a mean of 635.7 ± 8.5 per minute, P-R intervals from 0.03 to 0.05 seconds with a mean of 0.038 ± 0.00077 seconds, R_2 waves with a height from 0.4 to 1.3 millivolts with a mean of 0.714 ± 0.045 millivolts, and T_2 waves from 0.15 to 0.37 millivolts with a mean of 0.254 ± 0.011 millivolts.

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INTESTINAL OBSTRUCTION: THE ROLE OF INFECTION IN PERFORATION OF THE COLON*

EDGAR J. POTH AND JOHN N. MCCLURE, JR.

Perforation of the bowel is a frequent consequence and complication of intestinal obstruction, the ultimate cause of which is ischaemia and the resulting necrosis of the bowel wall. Increased intraluminal pressure of mechanical obstruction tends to lower the blood flow in the wall of the viscus. Infection, likewise, is an important adjuvant in this process. As the blood supply is embarrassed, bacteria invade the wall of the bowel with the elaboration to toxic substances which favor thrombosis of the arterial and venous capillaries to cause further vascular damage, ischaemia and necrosis.

PROCEDURES

This study deals with the consequences of ligating either the arteries, the veins, or simultaneously the arteries and veins to segments of distal ileum with and without the attenuation of the bacterial flora of the intestine by the administration of sulfasuxidine or sulfathalidine. One hundred eleven healthy, adult mongrel dogs were divided into six groups as indicated in Table I.

All animals received ground horse meat for twelve days before the interruption of the blood vessels and again for twelve days beginning 48 hours after the operation. The control animals were fed only meat while the treated animals received sulfasuxidine or sulfathalidine mixed with the meat ration. The drugs were administered (1 gram of sulfasuxidine per kilo of body weight or 0.5 gram of sulfathalidine per kilo of body weight each 24 hours) mixed with the meat and divided into six portions given at four-hour intervals. Dogs weighing approximately ten kilograms were selected.

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*From the Surgical Research Laboratory, The University of Texas Medical Branch.

TABLE I

All animals received ground horse meat in six daily feedings for two weeks before ligation of the arteries, veins, or simultaneously the arteries and veins to a distal segment of ileum. Groups D, E, and F received oral sulfonamides.

Group	Table	No. of Animals	Deaths Per Cent				Procedure
			48 Hrs. or Less	3 to 5 Days	6 to 10 Days	More Than 10 Days	
A	II	12	50	33	17	0	No drug therapy. Arteries doubly ligated and divided.
B*	III	9	100	0	0	0	No drug therapy. Veins doubly ligated and divided.
C	IV	12	58	17	0	25	No drug therapy. Arteries and veins doubly ligated and divided simultaneously .
D†	V	35	17	32	6	45	Sulfasuxidine or sulfathalidine orally for two weeks prior to double ligation and section of the arteries. Sulfonamides started again on p.o. day two and continued for ten days.
E*	VI	7	30	0	0	70	Same as D, except that the veins are doubly ligated and divided.
F†	VII	36	22	22	11	45	Same as D, except that arteries and veins are divided simultaneously.

*It is interesting that the death rate is higher in these groups than in any other during the first 48 hours, although in the treated Group *E* the ultimate survival is greater than in Groups *D* and *F*. These observations would indicate that the blood loss into the local tissues probably contribute to the early deaths when the veins only are ligated.

†The final survival rates in Groups *D* and *F* are identical. This observation would indicate that the ligation of the veins simultaneously with the interruption of the accompanying artery has no beneficial effect.

At operation a segment of distal ileum, ten cm. proximal to the antimesenteric artery, was isolated and the blood vessels doubly ligated and divided near the root of the mesentery. The leaf of the mesentery was split along the limiting boundaries, and the blood vessels coursing in the mesenteric fat, parallel to the bowel, were doubly ligated and divided. The length of segment taken was five cm. per kilo of body weight with a maximum length of fifty cm. even though the dog weighed more than ten kilograms.

The various groups of animals were observed for survival rates and morbidity. Finally all surviving animals were sacrificed and autopsied. The results of these experiments are summarized in Tables I to VII.

Discussion

The lesion which ultimately caused necrosis and perforation of the bowel was ischaemia. The deficiency of blood supply was caused not only by the mechanical ligation of blood vessels but was augmented by progressive intravascular clotting. The degree of clotting was heightened by the invasion of the bowel wall by bacteria and their elaboration of toxins. The difference observed between the control and treated animals is interpreted as the effect of the sulfonamides in attenuating the bacterial flora within the lumen of the bowel and the consequent prevention of invasion of the wall of the gut. This effect is sufficient to protect against thrombosis, necrosis, and perforation.

The therapeutic implications are that sulfasuxidine and sulfathalidine, as well as other antibacterial substances active locally in the bowel, should be of value where the tissues may be subjected to invasion by the intestinal flora such as may occur in mesenteric thrombosis and following surgical procedures on the bowel. These compounds have been given prophylactically in the former condition, but our experience is too limited to warrant conclusions. In the latter instance, however, there has been both clinical and experimental evidence that the alteration of the bacterial flora effected by the oral administration of these sulfonamides favors healing of lesions of the bowel.

TABLE II

Group A: Tabulation of results of the division of the arteries to segments of distal ileum of a group of control animals.

Animal No.	Weight in Kg.	Length of segment	Lived	Comments
1	10	50 cm.	14 hrs.	Died. Large perforation with massive peritonitis.
6	10	50 cm.	30 hrs.	Died. Large perforation with much free fluid in peritoneal cavity. Diffuse crepitus in viscera and walls.
24	9	40 cm.	36 hrs.	Died. Much free fluid; autolysis with large perforation; massive peritonitis.
16	18.5	50 cm.	36 hrs.	Died. No perforation; much free fluid; massive peritonitis.
7	9	25 cm.	48 hrs.	Sacrificed. Was very ill. Large walled off perforation; much free fluid in cavity.
22	13.5	50 cm.	48 hrs.	Died. Much free fluid; autolysis with large perforation; massive peritonitis.
10	10	50 cm.	50 hrs.	Sacrificed. Large perforation of gut. Would have died shortly. Massive peritonitis; much free fluid.
11	11	35 cm.	3 days	Sacrificed. Large perforation of gut, walled off, much free fluid. Would have died.
20	10	50 cm.	3 days	Died. Much free fluid; large perforation; massive peritonitis.
18	11	50 cm.	4 days	Died. Large perforation. Much free fluid; massive peritonitis.
13	10.5	25 cm.	1 week	Sacrificed. Was doing well. Reaction subsiding, would have recovered. Short segment.
23	11	50 cm.	10 days	Died. Much free fluid, complete obstruction, adhesion and volvulus. No perforation.

TABLE III

Group B: Tabulation of results of the division of the veins to segments of distal ileum of a group of control animals.

Animal No.	Weight in Kg.	Length of segment	Lived	Comments
76	7.0	35 cm.	12 hrs.	Extensive peritonitis; large multiple perforations of loop.
3	11.0	50 cm.	18 hrs.	Sacrificed. Would have died shortly. Much free fluid, autolysis, large perforation, and massive peritonitis.
80	7.5	38 cm.	30 hrs.	Extensive peritonitis; loop necrotic and perforated.
78	8.0	40 cm.	34 hrs.	Extensive peritonitis with perforations.
82	10.0	50 cm.	35 hrs.	Extensive peritonitis with perforations.
90	12.5	50 cm.	35 hrs.	Widespread peritonitis with large perforations.
88	12.0	50 cm.	37 hrs.	Peritonitis and perforations.
86	10.0	50 cm.	37 hrs.	Peritonitis and perforations.
84	10.0	50 cm.	45 hrs.	Peritonitis and perforations.

TABLE IV

Group C: Tabulation of results of the simultaneous interuption of both arteries and veins to segments of distal ileum of a group of control animals.

Animal No.	Weight in Kg.	Length of segment	Lived	Comments
4	10	50 cm.	30 hrs.	Sacrificed. Necrosis but no gross perforation. Crepitus extensive in peritoneal cavity and abdominal wall.
5	6.5	50 cm.	30 hrs.	Sacrificed. Large perforation with massive peritonitis.
2	9.5	50 cm.	36 hrs.	Sacrificed. Autolysis of segment with perforation and massive peritonitis.
9	14	30 cm.	36 hrs.	Sacrificed. Very large dog. Autolysis of segment. Massive peritonitis with crepitus.
25	10	50 cm.	36 hrs.	Sacrificed. Much free fluid; autolysis with large perforation and massive peritonitis.
12	8	40 cm.	36 hrs.	Sacrificed. Much free fluid; large perforation walled off.
19	9	50 cm.	48 hrs.	Sacrificed. Much free fluid; massive peritonitis; segment very dark and soft; no perforation.
8	10	25 cm.	50 hrs.	Sacrificed. Might have lived. No perforation; little free fluid. Mass well walled off.
21	10	50 cm.	3 days	Sacrificed. Much free fluid; autolysis with large perforation; massive peritonitis.
17	8	40 cm.	2 weeks	Died. Cause unknown. Peritoneum clean; some adhesions, no obstruction.
14	11	25 cm.	2 weeks	Sacrificed. Was doing well. Peritoneum clean, healing well. Would have survived.
15	16	50 cm.	7.5 mos.	Sacrificed for photograph. Only control dog to live. Well healed; omentum adherent to bowel.

TABLE V

Group D: Tabulation of results of the division of the arteries to segments of distal ileum of a group of animals which had received oral sulfasuxidine or sulfathalidine preoperatively and postoperatively.

Animal No.	Weight in Kg.	Length of segment	Lived	Comments
61	10	50 cm.	12 hrs.	Photographed q 2h x 6 for 12 hours and then sacrificed.
71	10.5	50 cm.	24 hrs.	Sacrificed for photograph. Much fluid; massive peritonitis; numerous adhesions. Segment discolored. No gross perforation. Might have survived.
7	11	50 cm.	36 hrs.	Sacrificed. Massive peritonitis; much fluid no gross perforation. Might have lived.
16*	8	50 cm.	36 hrs.	Died. Much free fluid; massive peritonitis. Large perforation in center.
17*	7.5	50 cm.	36 hrs.	Sacrificed. Much free fluid; massive peritonitis; autolysis with large perforation. Crepitus in viscera.
57	7.5	35 cm.	48 hrs.	Sacrificed. Intestines massed; segment discolored. No perforation; no peritonitis. Would probably have survived.
22	9	45 cm.	54 hrs.	Sacrificed. Much free fluid; massive peritonitis. Large perforation in center. Minimal adhesions.
32	11	50 cm.	55 hrs.	Sacrificed. Much free fluid; massive peritonitis; large perforation.
8	10	50 cm.	60 hrs.	Sacrificed. Much fluid; massive peritonitis, autolysis with perforation; crepitus in viscera. Gas bacillus infection.
10	12.5	50 cm.	60 hrs.	Sacrificed. Much free fluid; massive peritonitis. No gross perforation. Might have lived.
21	8	40 cm.	3 days	Sacrificed. Large perforation in center; much free fluid; massive peritonitis; numerous adhesions.
51	11	50 cm.	3 days	Sacrificed. Much fluid; massive peritonitis; large perforation; minimal adhesions.
63	10	50 cm.	3 days	Sacrificed. Much free fluid; massive peritonitis; autolysis with large perforation. Numerous adhesions.
68	11.5	50 cm.	4 days	Sacrificed for photograph. Little fluid. Segment and mesentery contracted. Numerous adhesions. Would have survived.

TABLE V—Continued

Animal No.	Weight in Kg.	Length of segment	Lived	Comments
31	13.5	50 cm.	4 days	Died. Emaciated. In poor condition; much free fluid; massive peritonitis; discoloration but no perforation.
27	11	50 cm.	5 days	Sacrificed. Much free fluid; massive peritonitis. Large perforation in center.
69	12	50 cm.	5 days	Sacrificed for photograph. Numerous adhesions; segment folded in mass; slight discoloration; no obstruction; segment and mesentery contracted. Would have survived.
48	7.5	35 cm.	7 days	Sacrificed. Emaciated. Peritoneal cavity smooth; minimal adhesions; segment and mesentery contracted. Normal color except 1 cm. blue area in center. No peritonitis. Would have lived.
62	11.5	50 cm.	10 days	Sacrificed with CO for photograph. Numerous adhesions; normal color; segment and mesentery contracted. No obstruction.
3	9	50 cm.	11 days	Sacrificed. Normal color. Peritoneum smooth. No obstruction. Had severe skin infection.
19	10	50 cm.	14 days	Sacrificed. Complete obstruction. Doubled on itself. Numerous vascular adhesions; small volume of free fluid.
49	14	50 cm.	14 days	Sacrificed for photograph. Peritoneum smooth; segment and mesentery contracted. Normal color; no obstruction. Minimal adhesions.
65	9.5	40 cm.	20 days	Sacrificed for photograph. Numerous adhesions; normal color; segment folded in mass; no obstruction. Vessels bridging ends of mesenteric stumps. Segment and mesentery contracted.
41	12	50 cm.	1 mo.	Died. Cause unknown. Peritoneum smooth. Bowel normal color; numerous adhesions.
44	11	50 cm.	1 mo.	Sacrificed for photograph. Numerous adhesions; normal color; segment and mesentery contracted.
47	7	35 cm.	1 mo.	Sacrificed for photograph. Minimal adhesions. Peritoneum smooth; segment and mesentery contracted. Normal color.

TABLE V—Continued

Animal No.	Weight in Kg.	Length of segment	Lived	Comments
38	9.5	50 cm.	1.5 mos.	Sacrificed for photograph. Numerous adhesions; segment and mesentery contracted. Numerous collateral vessels.
28	10	50 cm.	1.5 mos.	Sacrificed. Emaciated; had mange and no hair. Peritoneum smooth; minimal adhesions; no obstruction.
55	11	50 cm.	50 days	Sacrificed for photograph. Minimal adhesions, normal color; segment and mesentery contracted. No obstruction. Vessels bridging ends of mesenteric stumps.
40	11	45 cm.	2 mos.	Sacrificed with CO for photograph. Minimal adhesions; segment and mesentery contracted. Adhesions very vascular.
60	10	50 cm.	75 days	Sacrificed for photograph. Minimal adhesions; segment and mesentery contracted. Normal color; no obstruction.
33	13	50 cm.	6 mos.	Sacrificed. Peritoneum smooth; minimal adhesions; segment contracted; adhesions vascular.
2	9	50 cm.	7 mos.	Sacrificed with CO for photograph. Minimal adhesions in peritoneal cavity.
14*	13.5	50 cm.	8 mos.	Sacrificed for photograph and X ray. Minimal adhesion. Normal color; segment contracted.
9	11	50 cm.	9 mos.	Sacrificed for photograph. Numerous adhesions; segment contracted. Normal color, no obstruction.

*Received Sulfathalidine; others received Sulfasuxidine.

TABLE VI

Group E: Tabulation of results of the division of the veins to segments of distal ileum of a group of animals which had received oral sulfasuxidine preoperatively and postoperatively.

Animal No.	Weight in Kg.	Length of segment	Lived	Comments
83	12	50 cm.	24 hrs.	Extensive peritonitis with multiple perforations.
79	9.0	45 cm.	48 hrs.	Extensive peritonitis with perforations.
77	6.5	35 cm.	30 days	Sacrificed. Condition good, shortened, normal appearing bowel. Many adhesions.
81	6.0	30 cm.	30 days	Sacrificed. Condition good. Moderate number of adhesions. Bowel segment shortened; normal appearance.
85	11.0	50 cm.	50 days	Sacrificed. Condition good. Moderate number of adhesions. Bowel segment appeared normal except for shortening of both mesentery and viscus.
87	10.0	50 cm.	50 days	Well until sacrificed. Mesentery and bowel shortened, otherwise normal.
89	10.5	50 cm.	50 days	Well until sacrificed. Normal except for adhesions and shortening of mesentery and bowel segment.

TABLE VII

Group F: Tabulation of results of the simultaneous division of both arteries and veins to segments of distal ileum of a group of animals which had received oral sulfasuxidine preoperatively and postoperatively.

TABLE VII

Group F: Tabulation of results of the simultaneous division of both arteries and veins to segments of distal ileum of a group of animals which had received oral sulfasuxidine or sulfathalidine preoperatively and postoperatively.

Animal No.	Weight in Kg.	Length of segment	Lived	Comments
58	8.5	45 cm.	19 hrs.	Sacrificed. No peritonitis or fluid. Segment discolored. Might have survived.
4	7	50 cm.	36 hrs.	Sacrificed. Free fluid; no perforation; peritonitis. Might have survived.
18	7.5	50 cm.	36 hrs.	Sacrificed. Much fluid; massive peritonitis; large perforation in center of segment; numerous adhesions.
12	7.1	50 cm.	48 hrs.	Sacrificed. Much free fluid; massive peritonitis; autolysis with perforation.
64	10	50 cm.	48 hrs.	Sacrificed. Massive peritonitis; much fluid; autolysis with large perforation of segment; numerous adhesions.
13*	15.5	60 cm.	48 hrs.	Sacrificed. Much fluid; massive peritonitis; autolysis with perforation.
53	9.5	45 cm.	48 hrs.	Sacrificed. Much fluid; massive peritonitis, normal color; no perforation. Might have survived.
46	9	40 cm.	48 hrs.	Sacrificed. Much fluid; massive peritonitis; no perforation. Might have survived.
25	10	50 cm.	50 hrs.	Sacrificed. Much fluid; massive peritonitis; autolysis with large perforation; no adhesions.
30	10	50 cm.	3 days	Sacrificed. Much fluid; massive peritonitis; autolysis with large perforation.
37	14	50 cm.	3 days	Sacrificed. Much fluid; massive peritonitis; segment discolored; no perforation. Might have survived.
54	8	40 cm.	3 days	Sacrificed. Much fluid; peritonitis. Strangulation of loop and dilation of proximal bowel.
59	8.2	42 cm.	3 days	Sacrificed. Volvulus of segment. Massive peritonitis; much fluid; autolysis with large perforation of segment; numerous adhesions.
74	12	50 cm.	3 days	Sacrificed for photograph. Segment massed by omentum. Slight discoloration; no peritonitis. Dog alert and active. Probably would have survived.
15*	9	50 cm.	5 days	Sacrificed. Much fluid; massive peritonitis; large perforation in center of segment; numerous adhesions.
39	11	50 cm.	5 days	Sacrificed. Much fluid; massive peritonitis; large perforation at proximal end.
70	12	50 cm.	6 days	Sacrificed for photograph. Numerous vascular adhesions. Segment masses; slight discoloration; segment and mesentery contracted. Probably would have survived.
72	7.5	37 cm.	7 days	Sacrificed for photograph. Minimal adhesions; segment and mesentery contracted; normal color. No fluid. Would have survived.

TABLE VII—Continued

Animal No.	Weight in Kg.	Length of segment	Lived	Comments
35	9.5	50 cm.	9 days	Emaciated; general debilitation. Bowel normal color; no peritonitis; no obstruction.
75	15.5	50 cm.	10 days	Sacrificed for photograph and X ray. Numerous vascular adhesions. Segment enveloped in mass, shortened. Slightly discolored. Would have survived.
52	11	50 cm.	12 days	Sacrificed for photograph. Numerous adhesions, normal color; segment and mesentery contracted.
66	9.5	40 cm.	14 days	Sacrificed with CO for photograph. Numerous adhesions; vascular. Segment and mesentery contracted. Normal color.
73	11	50 cm.	18 days	Sacrificed. Complete obstruction at end of segment, which folded on self. Slight discoloration. Well healed, no perforation.
34	9.5	45 cm.	1 mo.	Sacrificed. Vulvulus proximal to operation site, which was well healed.
43	14	50 cm.	1 mo.	Sacrificed for photograph. Numerous adhesions, vascular; segment and mesentery contracted; folded in mass. No obstruction.
45	11.5	50 cm.	1 mo.	Sacrificed for photograph. Numerous adhesions, vascular; segment and mesentery contracted; vessels bridging mesenteric segments. No obstruction.
67	8	37 cm.	1 mo.	Sacrificed for photograph. Numerous vascular adhesions. Segment and mesentery contracted. Normal color.
42	10	40 cm.	1.5 mo.	Sacrificed for photograph. Minimal adhesions; segment contracted; bridges around ends of mesenteric vessels.
36	9.5	45 cm.	100 days	Sacrificed for photograph. Minimal adhesions; segment contracted; bridges around ends of mesenteric vessels.
5*	6.4	50 cm.	4 mos.	Killed in fight. Gained weight; minimal adhesions; segment contracted.
26	10	50 cm.	5 mos.	Sacrificed for photograph. Minimal adhesions; segment and mesentery contracted. Normal color.
29	7.5	35 cm.	5.5 mos.	Sacrificed for photograph and X ray. Minimal adhesions; segment contracted. Collateral vessels around ends of severed ones.
20	8	40 cm.	7 mos.	Killed in fight. Minimal adhesion. Peritoneum smooth; bowel not contracted.
24	10	50 cm.	8 mos.	Sacrificed for photograph. Minimal adhesions; segment contracted; mesentery also shortened.
11	9.5	50 cm.	8 mos.	Sacrificed for photograph and X ray. Minimal adhesions; segment contracted; normal color.
6*	11	50 cm.	9 mos.	Sacrificed for photograph and X ray. Numerous vascular adhesions; segment contracted.

*Received Sulfathalidine; others received Sulfasuxidine.

Summary

A study of the survival rate following vascular damage of segments of ileum demonstrates the beneficial effect of the administration of sulfasuxidine and sulfathalidine. The role of the intestinal flora in necrosis and repair of bowel is emphasized.

*Received Sulfathalidine; others received Sulfasuxidine.

them contracted.

THE EFFECT OF TETRAETHYLTHIURAMDISULPHIDE (ANTABUSE) ON CELLULAR RESPIRATION*

THOMAS P. EDWARDS

Hald, Jacobsen, and Larsen (1948) have described the sensitizing effect of tetraethylthiuramdisulphide (Antabuse) to ethyl alcohol in human subjects. The characteristic symptoms shown by the sensitized patient following injection of relatively small amounts of alcohol include a feeling of heat and intense flushing in the face, neck, and arms, palpitations, dyspnea, tachypnea, nausea, vomiting, and headache. The pulse rate is increased and there is a fall in the systolic and diastolic blood pressures. These symptoms and signs can be fully explained by an increased concentration of acetaldehyde in the blood, which occurs uniformly after the taking of alcohol by patients previously treated with Antabuse (Asmussen, Hald, Jacobsen, 1948). This was directly confirmed in cases where acetaldehyde was infused intravenously.

Since this drug, now on trial as a remedy for alcoholism, has impressed some authors (Bell and Smith, 1949; Jones, 1949) with the inordinate severity of the reaction experienced by some patients as a result of Antabuse-alcohol combination, and since the fundamental action of the drug is unknown, further investigation of the effecct of Antabuse on metabolic processes is warranted. It seemed of importance to investigate at first the influence of Antabuse upon cellular respiration, in order to see whether or not it intervenes in the Warburg-Keilin system.

METHODS

The cellular respiration was measured by oxygen uptake with the Warburg technique. Each flask contained 1 ml. of homogenate, 0.5 ml. of propylene-glycol solution of Antabuse,

*From the Department of Neuropsychiatry and the Tissue Culture Laboratory, The University of Texas, Medical Branch, Galveston. Received for publication August 30, 1949. This investigation was undertaken at the suggestion of Dr. W. W. Nowinski, whose help and encouragement is gratefully acknowledged. Aided by a grant administered by C. M. Pomerat from the U. S. Public Health Service, No. RG 333(c2).

and 1.1 ml. of Sorensen phosphate buffer at pH 7.2.[1] The controls contained the same amount of solutions, but the propylene glycol-water solution was substituted for Antabuse. (It was shown that propylene glycol does not affect the rate of respiration.) The center cups contained 0.4 ml. of 20% KOH. Filter papers were added, according to Dixon and Elliott (1934).

The homogenate of rat liver (10 per cent) in ice cold Sorensen phosphate buffer was prepared according to the technique described by Potter (1948). Antabuse solution was prepared by saturating 15 ml. of propylene glycol with crystalline antabuse powder, ground in a mortar. The solution was then diluted with 5 ml. water (or buffer), mixed well, filtered, and kept at room temperature until ready for use. The clear filtrate gave a yellow color with $CuSO_4$ indicating the presence of Antabuse in solution. A 3:1 solution of propylene glycol and water (or buffer) was prepared for the controls.

Pure oxygen was passed through the manometers for 3 to 5 minutes, which were equilibrated for 7 to 10 minutes in Warburg apparatus at 38° C. Readings were taken at 10-minute intervals for a period of one hour.

The figures are expressed in cmm. oxygen uptake per hour, per 1 ml. of 10% homogenate.

Results

Four series of experiments were carried out, the results of which are summarized in Table I. Throughout all the experiments the inhibitory effect of Antabuse on oxygen consumption was marked. The averages of single series were — 11.10; — 10.02; — 9.74; and — 11.61, respectively, for the homogenate with Antabuse. The corresponding averages for the controls (which did not contain the drug) were — 86.35; —72.69; — 55.60; and — 72.16. These results show clearly that there is a definite inhibition of oxygen uptake of liver homogenate, which, expressed in percentage inhibition amounts to 83–87 per cent. The average of all our results show a value

[1]The addition of the Antabuse solution caused a precipitation of a portion of the drug, but qualitative tests with $CuSO_4$ after the experiments gave a strong yellow color.

of —10.54 with added Antabuse, against —70.94 for the controls. This gives an average inhibition of 85 per cent.

TABLE I

Oxygen uptake in cmm. of 10% homogenate with and without Antabuse (calculated per 1 hour per 1 ml. homogenate).

Series I		Series II		Series III		Series IV	
Plus Antabuse	Control	Plus Antabuse	Control	Plus Antabuse	Control	Plus Antabuse	Control
—17.44	—113.26	— 3.92	—67.64	—11.45	—54.81	—16.36	—101.79
—11.00	— 77.74	— 6.93	—82.74	— 1.93	—59.48	—21.21	— 67.60
— 4.86	— 79.25	—14.67	—88.26	— 8.12	—61.54	— 4.06	— 81.05
	— 75.17	— 5.53	—54.45	—18.45	—45.82	— 7.69	— 64.78
		—19.82	—60.36	— 7.51	—56.59	—24.03	— 45.59
		— 5.68		— 6.19		— 3.10	
		—13.56		—14.53		— 4.85	
Average	Average	Average	Average	Average	Average	Average	Average
—11.10	— 86.35	—10.02	—72.69	— 9.74	—55.60	—11.61	— 72.16
87% inhibition		86% inhibition		83% inhibition		84% inhibition	

Average oxygen uptake of all experiments with Antabuse.. —10.54
Average of all controls..... —70.94
Average inhibition 85%

DISCUSSION

The described results indicate that Antabuse in concentrations used exerts an inhibitory influence upon cellular respiration. Whether or not this effect is related to the sensitizing ability of this drug in vivo remains to be seen. In spite of the unusually high blood acetaldehyde levels seen after Antabuse-alcohol administration, the elimination rate of alcohol, as measured by blood alcohol levels, is the same in normal individuals and in those treated with Antabuse (Hald and Jacobsen, 1948). Furthermore, experiments in animals have shown that acetaldehyde is eliminated at the same rate, regardless of whether the animals had been treated with Antabuse or not. This is in accord with the fact that patients treated with Antabuse alone show no increase in blood acetaldehyde level (Hald and Jacobsen, 1948).

These results suggested to Hald and Jacobsen the possibility that only a part of ingested alcohol breaks down to acetaldehyde, and that Antabuse acts by partially or completely blocking another, as yet unknown, pathway of alcohol metabolism.

Consequently, a higher proportion of alcohol is oxidized to acetaldehyde. We suggest the possibility that Antabuse is broken down in the body, thus releasing the cyanide (or cyanate) groups contained in the thiuram nucleus. The released cyanide would then act as an enzyme inhibitor. In favor of this supposition is the fact that only 20 per cent of Antabuse as such is excreted, *i.e.*, that 80 per cent must be retained by the body. Furthermore, the result of our experiments point toward a far-reaching inhibition of respiratory enzymes, comparable to that of cyanide. Of importance also is the fact that cyanamide produces a hypersensitivity to alcohol similar to that seen with the Antabuse (Koelsch, 1914). Finally, there are certain symptoms in some patients treated with Antabuse which are manifested without ingestion of alcohol. Since the acetaldehyde level of the blood is not altered in these patients, there is the indication that a toxic substance is liberated.

Summary

The effect of tetraethylthiuramdisulphide (Antabuse) upon the oxygen consumption of rat liver homogenates was studied with the Warburg technique. The average figure (24 experiments) obtained for oxygen uptake of the homogenate plus Antabuse was — 10.54 cmm. per hour. The average figure (19 experiments) obtained for the oxygen uptake of the homogenate without Antabuse was — 70.94 cmm. per hour. This represents an inhibition of 85 per cent.

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CALLING ATTENTION TO

Items of Possible Interest to Our Friends

August, 1949

Light Summer Reading: B. J. Anson comments on Vesalian anatomical illustrations (*Surg. Gyn. Obs.*, 89/97/49). W. B. Cannon and A. Rosenblueth examine *Supersensitivity of Denervated Structures* (Macmillan, N.Y., 49, 270 pp., $6). W. Coutu describes *Emergent Human Nature* (Knopf, N.Y., 49, 400 pp., $5.50). V. Dabney exposes *Dry Messiah: The Life of Bishop Cannon* (Knopf, N.Y., 49, 350 pp., $4). J. Davenport compiles Slurvian lexicon (*New Yorker*, June 18/49, pp. 25). T. S. Eliot neglects science in his *Notes Towards the Definition of Culture* (Harcourt Brace, N.Y., 49, 128 pp., $2.50). R. Hillyer castigates poetical snobbery, treason, T. S. Eliot, and C. G. Jung's Bollingen psychiatry retreat (*Sat. Rev. Lit.*, June 11 and 18/49). J. Hubley analyses scientific perversion of Lysenko's genetic authoritarianism (*Nature*, 163/942, 974/June 18, 25/49). G. Jefferson philosophizes on mind, machine, and man (*Brit. Med. J.*, 1/1105/June 25/49). C. Lamont offers *Humanism as a Philosophy* (Phil. Lib., N.Y., 49, 368 pp., $3.75). Sly H. L. Mencken resurrects grab-bag full of old wise-cracks (*A. Mencken Chrestomathy*, Knopf, N.Y., 49, 627 pp., $5). L. E. Read condemns thinking by proxy in stimulating "On That Day Began Lies" (*In Brief*, 3/1/49, Found. Economic Educ., Irvington, N.Y.). A. Schweitzer, great humanist, offers for festival *Goethe: Four Studies* (Beacon, Boston, 49, 150 pp., $2.50). M. L. Starkey finds *The Devil in Massachusetts: A Modern Inquiry into the Salem Witch Trials* (Knopf, N.Y., 49, 300 pp., $3.50). UNESCO holds conference on medical abstracting (*Brit. Med. J.*, 1/1091/June 18/49).

Basic Business: K. B. Augustinsson and D. Nachmansohn find tetraethyl-pyrophosphate most powerful inhibitor of acetylsholine esterase (*J. Biol. Chem.*, 179/543/49). L. Bakay and O. Lindberg, using P_{32}, show brain tissues exchange P via cerebrospinal fluid, while hypophysis and hypothalamus via blood (*Acta Physiol. Scand.*, 17/179/49). F. R. Bettley and M. P. Spence show phenylbenzyl-aminomethyl imidazoline (Antistin-Ciba) is antiprurtic independently of anti-allergic action (*Acta Dermat.*, 29/266/49). G. Biorck finds 3% dry wt. skeletal muscle is myoglobin, 1% heart, and 0.25% non-pregnant uterus (*Acta Med. Scand.*, 1/33/Suppl., 226/49, 216 pp.). W. Buschke discusses factors influencing intercellular cohesion (*J. Cell. Comp. Physiol.*, 33/145/49). P. Fildes leads discussion on antibiotic activity of growth factor analogues (*Proc. Roy. Soc. B.*, 136/145/49). A. Goldstein reviews interactions of drugs and proteins (*Pharmacol. Rev.*, 1/102/49). R. Grant and others find epinephrin causes atrial fibrillation via reflex vagal excitation (*Am. Heart J.*, 37/1081/49). J. Gross observes chemically and structurally distinct threads and binder in elastic fibers (*J. Exp. Med.*, 89/699/49). C. M. Gruber

and others analyse action of Parpanit, diethylaminoethyl-phenylcyclopentane carboxylate (effective in Parkinsonism, R. Domenjoz, *Schw. Med. Wchnschr.*, 76/1282/46) in antagonizing acetylcholine (*J. Pharmacol. Exp. Th.*, 96/11, 42/49). H. T. Hanson and E. L. Smith find zinc aminopeptidase enzyme, carnosinase, which hydrolyses carnosine (*J. Biol. Chem.*, 179/789/49). A. V. Hill analyses work and heat of muscle contraction (*Proc. Roy. Soc. B.*, 136/195–254/49). K. Hohl and H. R. Schmiz review chemotherapy of cancer (*Schw. Med. Wchnschr.*, 79/421/May 14/49). R. H. Horrocks and G. B. Manning describe chromatographic methods for identifying reducing substances in urine (*Lancet*, 1/1042/June 18/49). P. Harroun and C. W. Fisher note curare does not pass placenta nor inhibit uterine contractions (*Surg. Gyn. Obs.*, 89/73/49). E. Kalonen finds hyaluronidase in testis is factor in fertility (*Acta Physiol. Scand.*, 17/170/49). D. Keilin and E. F. Hartree discuss succinic dehydrogenase-cytochrome enzyme system (*Biochem. J.*, 44/205/49). A. Kristenson notes variations in lymphocyte size in health and disease (*Acta Med. Scand.*, 133/157/49). S. Lagerstedt shows basophilic cytoplasmic inclusions in liver cells disappear in starvation and build up on high protein diet from ribonucleic acid proteins near nuclear membrane under influence of nucleolus (*Acta Anat.*, 7/Suppl., 9/49, 116 pp.). J. Lorch shows protein complexes as well as phosphatase are involved in bone formation (*J. Bone and Jt. Surg.*, 31/94/49). J. MacLeod and others note high genetic and muscular toxicity of lithium salts (*Am. J. Physiol.*, 157/177/49). R. A. Ormsbee and others show by radiactive S that mustard gas combines with carboxyl groups of skin proteins (*Arch. Biochem.*, 21/301/49). Our E. L. Porter and P. S. Wharton analyse nerve irritability after ischemia (*J. Neurophysiol.*, 12/109/49). F. J. W. Roughton and J. C. Kendrew edit *Haemoglobin* containing conference papers honoring memory of Sir Joseph Barcroft (Interscience, N.Y., 49, 320 pp., $8.50). K. Salomon and others describe visual disturbances fr. 330 mgm. mescaline orally and its urinary excretion (*J. Pharmacol. Ex. Th.*, 95:1/455/49). G. F. Saltzman reviews borigin of blood platelets (*Acta Med. Scand.*, 132/Suppl. 221/49, 98 pp.). A. M. Schwartz and J. W. Perry discuss *Surface Active Agents: Their Chemistry and Technology* (Interscience, N.Y., 49, 588 pp., $10). Note excellent Symposium on chemistry, physiology and pathology of blood pigments (*Deutsch. Arch. Klin. Med.*, 195/357–450/49). B. L. Vallee and J. C. Gibson note zinc content of blood constituents correlates with carbonic anhydrase activity (*Blood*, 4/455/49). H. H. Ussing discusses transport of ions across cellular membranes (*Physiol. Rev.*, 29/127/49). C. E. A. Winslow and L. P. Herrington review *Temperature and Human Life* (Princeton Press, Princeton, 49, 286 pp., $3.50).

SEPTEMBER, 1949

RAISED EYEBROW DEPT.: How did tough-minded Swiss editors fall for yachtman and color-photographer M. Curry's iodide gadget for estimating variations in "aran," hypothetical atmospheric factor influencing sense of well-being (*Schw. Med. Wchnschr.*, 79/668/July 23, 1949)?

GENERAL: C. Elze discusses J. Sylvius (1478–1555) as originator of anatomical nomenclature (*Ztschr. Anat. Entwick.*, 144/247/49). R. G. McCarthy and E. M. Douglass analyze *Alcohol and Social Responsibility* (Crowell, N.Y., 49, 320 pp., $3.50). Osler Centenary comments appear (*Brit. Med. J.*, 2/41–48/July 9, 49; *Arch. Int. Med.*, 84/1–198/49; *Bull. Johns Hopkins Hosp.*, 85/1–114/49, and fine series edited by Mrs. J. C. Trent, *N. Carolina Med. J.*, 10/377/49). B. Russell discusses *Authority and the Individual* (Allen and Unwin, London, 49, 125 pp., 6s). R. Sereno, in commenting on "Bricua," Porto Rican language, shows political influence of medicine (*Psychi.*, 12/167/49). U.S. Atomic Energy Commission issues *Atomic Energy and the Life Scienecs* (Supt. Docu., U.S. Govt. Printing Off., Washington 25, 49, 203 pp., $.45). M. B. Visscher Committee reports on civil liberties of scientists (*Science*, 110/177/Aug. 19/49).

CLINICAL: S. Bayne-Jones suggests hospitals as centers for preventive medicine (*Ann. Int. Med.*, 31/7/49). B. Beskow shows greater incidence of adolescent nervous symptoms in prematures than in normals (*Acta Pedi.*, 37/125/49). G. S. Campbell and others show increased intracranial pressure causes bradycardia, low cardiac output, and increased pulmonary blood pressure sufficient to cause edema preventable by atropine (*Am. J. Physiol.*, 158/96/49). W. S. C. Copeman shows relation of fibro-fatty tissue to rheumatic symptoms (*Brit. Med. J.*, 2/191/July 23/49). W. C. Diefenbach and J. K. Meneely recommend multiple dosage for digitalization (*Yale J. Biol. Med.*, 21/421/49). O. Gilje reviews etiology and therapy of leg ulcers (*Acta Dermat.*, 29/Suppl. 22/328 pp. 49). T. Gilman and I. L. Chaikoff suggest circulatory factors in liver fibrosis (*Arch. Path.*, 48/67/49). M. Gunther and J. E. Stainer find diurnal variations in fat content of breast milk independent of food intake (*Lancet*, 2/235/Aug. 6/49). H. Harris and A. Shuhman note blocking of antibodies (*Med. J. Austral.*, 1/828/June 25/49). H. J. Heite discusses statistical appraisal of clinical results (*Klin. Wchschr.*, 27/289/May 1/49). W. Hopker analyses clinical physiology of kidney disorders (*Arzt. Forsch.*, 3/321/July 10/49). C. T. Javert considers pathogenesis of endometriosis (*Cancer*, 2/399/49: this periodical too slick?). J. E. Mackinnon reports coccidioidal granuloma from Paraguay and Argentina (*An. Inst. Hyg. Montevideo*, 2/74/49). J. Mayer quantitates ageing by reorientation of food utilization to fat rather than to protein synthesis (*Growth*, 13/97/49). H. M. Jones makes clinico-genetic study of paralysis agitans (*Acta Psych. Neurol.*, Suppl. 54, 195 pp., 49). N. B. Myant and others show normal thyroid clears iodide fr. 16 cc. plasma per minute (*Clin. Sci.*, 8/109/49). J. Newsome devises secretin test for pancreatic function (*Gastroenterol*, 74/257/49). G. Nylin recommends special beds in chronic heart disease (*Arch. Inst. Cardiol. Mex.*, 19/280/49). P. A. Owren describes cyclic agranulocytosis (*Acta. Med. Scan.*, 134/87/49). E. E. Pochin and F. F. Rundle find 85 per cent increase in adipose tissue in ocular muscle fibers in thyrotoxicosis (*Clin. Sci.*, 8/89/49). J. F. Rinehart and L. D. Greenberg note heart lesions from thiamine deficiency (*Arch. Path.*, 48/89/49). T. Rosebury reports on *Experimental*

Air-Borne Infection (Williams & Wilkins, Balt., 49, 229 pp., $4). O. E. Sandler finds batyl alcohol fr. yellow bone marrow active in erythropoieses (*Acta. Med. Scand.*, 133/Suppl. 225/72 pp./49). A. P. Thompson gives Lumleian Lectures on Problems of Ageing and Chronic Sickness (*Brit. Med. J.*, 2/300/Aug. 6/49). O. Teutschlaender describes lipoido-calcinosis where lipid deposition precedes calcium (*Beitr. Path. Anat.*, 110/402/49). B. H. Waksman reviews etiology of rheumatic fever (*Med.*, 28/143/49). P. M. West and J. Hilliard find high chymotrypsin inhibitor and low rennin inhibitor levels indicate active malignant process (*Ann. West. Med. Surg.*, 3/227/49; *Proc. Soc. Exp. Med. Biol.*, 71/169/49). H. Zondek and G. Wolfsohn report sluggish renal function in myxedema (*Schw. Med. Wchnschr.*, 79/623/July 9/49). S. Zubiran receives imposing Festschrift, including A. C. Ivy's note on pain in visceral disease (*Rev. Invest. Clin.*, 1/1–614/49). S. Zuckerman analyses menstrual cycle (*Lancet*, 1/2031/June 18/49).

PHARMACOLOGICAL: F. M. Berger shows methyl-amyl-hydroxymethyl dioxolane ("Glyketal") blocks spinal interneurons (*J. Pharmacol.*, 96/213/49). A. Hirsch and Atr. Mattick note action of "nisin," new antibiotic, in TB (*Lancet*, 2/190/July 30/49). W. Kalow finds phenyl methyl carbinol causes large bile flow in 300 mg./Kg. oral dose (*Arch. Exp. Path. Parmakol.*, 206/35/49). F. W. Klempere and others (confirmed by R. S. Grier and others) show beryllium inhibits alkaline phosphatase while magnesium stimulates (*J. Biol. Chem.*, 180/281, 289/49). M. H. Loveless and M. Dworin conclude Tremeton, Pyrabenzamine and Thephorin are best antihistaminics (*Bull. N.Y. Acad. Med.*, 25/473/49). C. G. Mackenzie and others show rapid metabolism of methionine with 25 per cent methyl carbon in expired air in 1 day (*J. Biol. Chem.*, 180/99/49). S. A. Waksman and others find advantages of neomycin over streptomycin against mycobacteria (*Am. Rev. TB.*, 60/78/49).

OCTOBER, 1949

CLINICAL: S. T. Anning says gravitational ulcers of legs are due to deep vein thrombosis (*Brit. Med. J.*, 2/458/Aug. 27/49). J. de Brux and C. Marchand emphasize ribonucleic acids in liver cell pathology (*Presse Med.*, 701/July 30/49). F. Bruns and W. Rummel note importance of cysteine in permeability of membranes (*Klin. Wchnschr.*, 27/399/June 15/49). R. Cannon shows extracellular water less in obese than in average women (*Presse Med.*, 657/July 16/49). K. K. Cheng suggests wide variety in origin and mechanism of synthesis of plasma protein (*J. Path. Bact.*, 61/23/49). P. F. Clark and others discuss influence of nutrition in experimental infection (*Bact. Rev.*, 13/99/49). D. M. Hegsted and others show absolute amount and ratio of iron and phosphorus in diet influence amount of iron absorbed (*J. Exp. Med.*, 90/147/49). C. Kayser reviews mechanisms of sleep (*J. Physiologie*, 41/11/49). I. Mann and others show dried mouse mammary cancer retains activity in tumor production (*Brit. Med. J.*, 2/255/July 30/49). E. E. Muirhead and others warn against iron overload

from too many transfusions (*Arch. Int. Med.*, 63/477/49). G. Schubert discusses physical and biological basis of betatron therapy (*Arzt. Forsch.*, 3/377/49). L. Sicher discusses change of life as a psychosomatic problem (*Am. J. Psychotherap.*, 3/399/49). E. R. Trethewis and P. A. Melvin consider prothrombin deficiency as a factor in spontaneous abortion (*Med. J. Austral.*, 2/189/Aug. 6/49). R. J. Williams and others discuss genetotrophic factors in alcoholism (*Arch. Biochem.*, 23/275/49).

BASIC: C. Auerbach analyses chemical mutagenesis (*Biol. Rev.*, 24/355/49). J. Balo and I. Banga find elastolytic enzyme in pancreatic juice (*Schweiz. Ztschr. Path. Bact.*, 12/350/49). M. Berthrong and others find Sertoli cells of testis produce estrogen (*J. Clin. Endocrin.*, 9/579/49). M. Bessis and M. Bricka describe ultrastructure of leucocytes (*Comp. Rend. Soc. Biol.*, 143/375/49). J. Boeke analyses problem of nerve synapse (*Acta Anat.*, 8/18/49). J. J. Bouchaert and F. Jourdan review cerebral circulation (*J. Physiologie*, 41/69A/49). P. M. Cotes and others conclude diabetogenic principle of anterior pituitary is a complex of growth and adrenocorticotrophic hormones (*Nature*, 164/209/Aug. 6/49). W. L. H. Duckworth gives Linacre Lecture on *Galen's Anatomy* (Heffer, Cambridge, 49, 42 pp., 6s). W. E. Ehrich and others indicate plasma cell and not lymphocyte is responsible for antibody formation (*J. Exp. Med.*, 90/157/49). S. J. Folley discusses biochemical aspects of mammary gland function (*Biol. Rev.*, 24/316/49). J. W. Foster describes *Chemical Activities of Fungi* (Acad. Press, N.Y., 49, 664 pp., $9.50). L. B. Jaques finds 0.009 mgms. heparin per 100 cc. normal blood by new routine method (*Acta Hematol.*, 2/188/49). R. Lorente de No finds quarternary ammonium bases in brain participating in nerve impulse (*J. Cell. Comp. Physical.*, 33, Suppl. 231 pp., 49). H. S. Mason and C. I. Wright show oxidation of dihydroxyphenylalanine by tyrosinase to melanin (*J. Biol. Chem.*, 180/235/49; question: do benzyl ethers of hydroquinone block?). L. Monne relates structure and function of neurones to mental activity (*Biol. Rev.*, 24/297/49). J. Needham edits fine *Hopkins and Biochemistry*, 1861–1947 for 1st International Congress of Biochemistry (Heffer, Cambridge, 49, 361 pp., 18s). M. Ruderfer suggests action as a measure of living phenomena (*Science*, 110/245/Sept. 9/49). Sir Charles Sherrington (aet. 94) offers a gleaming appreciation of Goethe (*Brit. Med. J.*, 2/449/*Aug.* 27/49). A. Sols reviews phosphates (*Rev. Esp. Fisiol.*, 5/59–129/49). D. Thomson and others discuss *Oral Vaccines and Immunization by Other Unusual Routes* (Williams & Wilkins, Balt., 49, 342 pp., $11). H. van Goor surveys properties, distribution, and significance for CO_2 transport, of carbonic anhydrase (*Ensymol.*, 13/75–164/49). G. G. Villela and others find thiamine distributes in brain like acetylcholine with most in nucleus caudatus and least in white matter (*Arch. Biochem.*, 23/81/49). G. Urdang discusses *Goethe and Pharmacy* (Am. Inst. Hist. Pharmacy, Madison, Wisc., 49, 76 pp.).

PHARMACOLOGICAL: P. Arnold and others suggest possible use of pentamethonium iodide in study and treatment of peripheral vascular disease

(*Lancet*, 2/408/Sept. 3/49). E. A. Falco and others suggest antimalarials are antagonists of purines and pteroylglutamates (*Nature*, 164/107/July 16/49). A. Fleckenstein and A. Hardt note permeability factors in action of local anesthetics and antihistaminics (*Klin. Wchnschr.*, 27/360/June 1/49). C. E. Frohman and H. E. Day show oxythiamine to be potent antagonist of thiamine (*J. Biol. Chem.*, 180/93/49). F. Jung and H. Renner study nitrite-hb reaction (*Arch. Exp. Path. Pharmakol.*, 206/459/49). H. Killian and J. Maurath suggest myanesin as relaxer in narcosis (*Deutsch. Med. Wchnschr.*, 74/946/Aug. 12/49). C. Levaditi confirms G. Domagk (*Deutsch. Med. Wchnschr.*, 60/256/1935) that thiosemicarbazone has antituberculosis action (*Presse Med.*, June 11/49/521). F. C. Macintosh and W. D. M. Paton show effects of organic bases in liberating histamine (*J. Physiol.*, 109/190/49). G. F. Otto and T. H. Maren report on chemotherapy of filariasis (*Am. J. Hygiene*, 50/92/49). Note symposium on antibiotics for B polymyxa (*Ann. N. Y. Acad. Sci.*, 51/853–1000/49). W. F. van Oettingen reviews biochemorphology of phenol and derivatives (*Nat. Inst. Health Bull.*, 190/1949, 408 pp., $0.70).

NOVEMBER, 1949

BOOKS BUMBLE ON: P. M. Aggeler and S. P. Lucia present *Hemorrhagic Disorders: A Guide to Diagnosis and Treatment* (Univ. Chicago, 49, 112 pp., $10). B. P. Babkin centennializes *Pavlov: A Biography* (Univ. Chicago, 49, 470 pp., $6). D. W. Barrow offers *Clinical Management of Varicose Veins* (Hoeber, N.Y., 169 pp., $5). L. Bauman surveys *The Diagnosis of Pancreatic Disease* (Lippincott, Phila., 49, 74 pp., $5). C. Binger essays *More About Psychiatry* (Univ. Chicago, 49, 192 pp., $4). E. M. Bridge offers *Epilepsy and Convulsive Disorders in Children* (McGraw-Hill, N.Y., 49, 670 pp., $8.50). C. Clapp says *Drinking's Not the Problem* (Crowell, N.Y., 49, 179 pp., $2.50). E. T. Engle edits *Menstruation and Its Disorders* (C. C. Thomas, Springfield, Ill., 49, 344 pp., $6.50). H. Kraus sets up *Therapeutic Exercises* (Thomas, Springfield, 49, 336 pp., $6.50). B. W. Lichtenstein presents *Neuropathology* (Saunders, Phila., 49, 474 pp., $9.50). M. Mead goes to town in *Male and Female: A Study of the Sexes in a Changing World* (Morrow, N.Y., 49, 477 pp., $5). N. E. Reich well surveys *Diseases of the Aorta* (Macmillan, N.Y., 49, 304 pp., $7.50). A. Smith and A. D. Herrick edit *Drug Research and Development* (Revere, N.Y., 49, 608 pp., $10). F. S. Taylor appreciates *The Alchemists* (Schuman, N.Y., 49, 256 pp., $4). P. E. L. Thomas offers *A Guide for Authors on Mss., Proof and Illustration* (Thomas, Springfield, Ill., 49, 85 pp., $1.50). M. Thompson memorializes I. P. Semmelweis (1818–65) in *The Cry and the Covenant* (Doubleday, Garden City, 49, 469 pp., $3.50). I. Veith presents *The Yellow Emperor's Classic of Internal Medicine* (Williams and Wilkins, Balt., 49, 268 pp., $5). F. L. Wright celebrates L. H. Sullivan in *Genius and the Mobocracy* (Duell, Sloan, N.Y., 49, 113 pp., $5).

CLINICAL: F. Becker and others enthuse over bioclimatic influences on autonomic nervous system (*Arzt. Forsch.*, 3/436/Sept. 10/49). F. Bern-

hard discusses recognition and management of hyperinsulinism (*Deutsch. Med. Wchnschr.*, 74/1048/Sept. 2/49). J. Berry and T. D. Spies review phagocytosis (*Med.*, 28/239/49). L. Brillouin discusses life, thermodynamics and cybernetics (*Am. Sci.*, 37/554/49). D. J. Dalton (Med. student) suggests eosinophils as etiologic factors in allergy (*Lancet*, 2/607/49). W. A. Dibden reviews hyperventilation syndrome (*Med. J. Austral.*, 2/409/Sept. 17/49). C. A. Doan surveys hypersplenism (*Bull. N. Y. Acad. Med.*, 25/625/49). A. D. Gillanders shows faster blood flow and higher venous pressure in pulmonary emphysema than in health (*Quart. J. Med.*, 18/263/49). E. M. Glaser studies changes in peripheral blood flow from warming and cooling (*J. Physiol.*, 109/366, 421/49). E. Kahane and J. Levy review choline activity (*J. Physiologie*, 41/183/49). G. Keynes notes favorable effects of thymectomy in myasthenia gravis (*Brit. Med. J.*, 2/611/Sept. 17/49). J. H. Means offers clues to origin of Grave's disease (*Lancet*, 2/543/Sept. 24/49). E. Mellanby shows phytic acid from cereals has anticalcifying action (*J. Physiol.*, 109/488/49). L. L. Miller and others show that plasma globulin is metabolized faster than albumin and that red blood cells maturate with synthesis of Hb in 3 to 5 days (*J. Exp. Med.*, 90/297/49). M. Prinzmetal and others show loss of myocardial contractility after coronary occlusion (*Ann. Int. Med.*, 35/424/49). H. S. Raper discusses problems of fat absorption (*Brit. Med. J.*, 2/719/Oct. 1/49). J. Steudel notes Goethe's regard for Hippocratic medicine (*Arzt. Forsch.*, 3/429/Sept. 10/49).

PHARMACOLOGICAL: D. Bovet and others study curare-acetylcholine antagonism (*Arch. Internat. Pharmaco.*, 80/137, 159, 172/49). J. F. J. Cade suggests lithium salts for psychotic excitement (*Med. J. Austral.*, 2/349/Sept. 3/49). N. W. Karr and E. L. Hendricks caution against rapid administration of ammonium cmpds. (*Am. J. Med. Sci.*, 218/302/49). M. Kiese studies toxicity of nitro aromatics (*Arch. Exp. Path. Pharmak.*, 206/505–583/49). J. E. Meinhard perspects chromatography (*Science*, 110/387/Oct. 14/49). Merck issues bibliography on cortisone (Rahway, 49, 39 pp.). H. Okamoto reports o-aminophenol in 5% sol. with dextrin IM 1–10 cc. daily improves tuberculosis (*Jap. Med. J.*, 1/422/48). J. C. Opsahl finds adrenal cortex hormones inhibit spreading action of hyaluronidase (*Yale J. Biol. Med.*, 21/487/49). K. Rodahl notes toxicity of vitamin A and relation to scurvy (*Nature*, 164/530/Sept. 24/49). H. O. Schild discusses pAx and competitive drug antagonism (*Brit. J. Pharmacol.*, 4/277/49). F. Serri notes fungicidal action of aerosporin (*Compt. Rend. Soc. Biol.*, 143/363/49). J. Sigwald finds new dibenzo-p-thiazine effective in parkinsonism (*Presse Med.*, 59/819/Sept. 17/49). Symposium on adrenals, important, Med. Sect., AAAS, Hotel Statler, N.Y., Dec. 28–29. Symposium on antibiotics (*J. Clin. Invest.*, 28/821–1037/49). C. H. Waddington and C. B. Goodhart say carcinogens are not accumulated by nucleoproteins, so that their mutagenic action is indirect (*Quart. J. Microsc. Sci.*, 90/209/49). J. L. Webb and others study metabolism of heart slices in relation to drug action (*Arch. Biochem.*, 22/444/49).

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